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THE THIRTY-FOURTH MAUDSLEY LECTURE: EMERGENT PATTERNS OF THE PATHOLOGY OF MENTAL DISEASE*

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I SHOULD like to express my deep gratitude to you, Mr. President, to the immediate Past President, Dr. L. C. Cook and to the Association for the great honour that has been bestowed upon me by your invitation to deliver a lecture in this august series. It is a custom that the lecturer should pay homage to Henry Maudsley to whose memory these lectures are dedicated: may I reserve my homage until we come to the active part Maudsley played in the course of events with which this lecture will be concerned.

For some time past I have been interested in the historical aspects of neuropathology, and I have chosen the subject for this lecture, because I thought that—at a time of breath-taking developments in all the sciences—a brief pause and a retrospective glance at the past may well help to resolve some of our present perplexities. Needless to say, what competence I have is in the somatic aspects of pathology, and it is with these, and especially cerebral pathology, that I shall mainly deal.

I propose to go back no further than the re-awakening of the scientific spirit during the Renaissance. What Antiquity† had to say of cerebral function was swept aside by the pneuma theory, the essence of which was that the substance of the brain is a mere capsule for the ventricles in which the incorporeal “animal spirits” reside. This concept has been wrongly attributed to Galen; according to Walter Pagel (1958) it had its origin in Christian-Patristic doctrines of the 4th century A.D. It suited scholastic thought well and was only demolished in 1543 by Vesalius in his *De Fabrica*. Vesalius found water in the ventricles and thus became the discoverer of the cerebrospinal

* Delivered (in slightly abbreviated form) before the Royal Medico-Psychological Association on 12 November, 1959.

† The ancient concepts of the brain and its relation to the mind have been recently described by Woollam (1958).

fluid. He transferred the activity of the animal spirits to the brain itself, although he did not publish detailed views on their function in the brain substance (Foster, 1901; Singer, 1952).

Figure 1 gives a typical illustration of the "pneuma" concept: fantasy and imagination are located in the anterior ventricles; they form the "sensorium commune", a term introduced by Aristotle to designate a central place of activity of the soul upon which all senses converge and from which perception, movement and the higher mental faculties radiate. Intelligence resides in the middle, and memory in the posterior ventricles. The vermis (i.e. the choroid plexus), operating between anterior and middle chambers, was thought, by alternate contraction and relaxation, to control the activities of the spirits in the different chambers. Much of this crude concept was due to ratiocination or, as Vesalius put it, "figments of men who had never studied the handiwork of God".* The localization of the "sensorium commune" may have been suggested by the strikingly preponderant growth of the frontal region in the human skull and brain. It is of interest that in our time Freeman and Watts (1942, 1950) have once again associated the frontal lobes with imagination and fantasy.

Descartes (1662), a hundred years after Vesalius, is the next important figure, although he was a philosopher and not a practising natural scientist. Hence all his assumptions were deductive, and, as Walter Riese (1958) has pointed out, the "modern reader must begin by renouncing his observational knowledge". As is well known, Descartes regarded the animal body as a machine to which in man alone was a rational immortal soul added, which took up residence in the pineal gland, chosen for its central position at the entrance of the ventricles and because it was only loosely attached to the rest of the brain. This gland and the ventricles were the reservoirs of the (now corporeal) animal spirits which are compared to air or a subtle fluid. In Descartes' system, the brain itself had but a shadowy existence, serving only as the centre for the hollow nerve tubes which connected with the periphery and opened into the ventricles through theoretically assumed orifices.

With Thomas Willis, and the publication of *Cerebri Anatome* in 1664 and *De Anima Brutorum* in 1672, we enter an entirely new epoch. This is not to deny that he was a child of his time who still largely adhered to the teaching of Hippocrates and his four humours. This admixed with fashionable iatrochemical terms (which, incidentally, he introduced into this country) makes curious reading, particularly in the chapters dealing with materia medica and with mania, melancholia and stupidity, where he describes the degeneration of the animal spirits by adjectives such as burning, obscure, thick, dark, dry and watery, acetous, corrosive, and sulphureous like the Stygian waters. Likewise he adopted the crude mechanical terms of iatrophysics; for example, when speaking of the invisible flame of the blood, and the explosion of animal spirits, of the inner chamber of the soul as fitted with dioptric mirrors, of the corpora striata as an objective glass and of the corpus callosum as a whitened wall.

He also adopted Galen's animal spirits, but, for him, as for Descartes, they had become corporeal: Willis describes them as "subtile bodies", as the "beaming forth of divers rays of light" and makes them "inspire and fill full the medullary trunks . . . like the chest of a musical organ which receives the wind to be blown into all the pipes". No doubt, again iatrophysics; but one gains the impression that, had he known of electricity, he would have

* Quotation from Foster (1901).

accepted the electric current as fulfilling the functions of the animal spirits.

Like Descartes to whom he more than once pays ardent tribute, he distinguishes an immortal rational soul, created by God only for man, from the corporeal (animal) soul, but both have their close association with different parts of the brain. Only emotions are excluded: with Aristotle and some of Willis's more recent predecessors he still attributed these to the heart.*

With all this we are less concerned than with Willis's discoveries and views on the anatomy and function of the brain, and here again our concern is less with the arterial circle to which Willis's name has been attached† or with his description of the cranial nerves than with cerebral anatomy‡ in its relation to mental and other important function.

Table I summarizes Willis's main observations and views relevant to our

TABLE I

Thomas Willis (1664)

"Animal spirits" secreted from the blood in cerebral and cerebellar cortex.

Caudate nucleus (first described by him) the seat of "sensus communis" and responsible for voluntary movement and perception.

Imagination in *corpus callosum*.

Memory in *cerebral cortex*, in which the "animal spirits" rest after activity.

Animal instinct in *middle of brain*.

Involuntary action in *cerebellum*.

theme. We note that the animal spirits are secreted from the blood within the cerebral and cerebellar cortex which are also their resting places. The process of creation is conceived of as a chemical one, not unlike that of alcohol fermentation, a view which Willis shared with Sylvius (1679), also like himself a leading iatrochemist.

Imagination is considered to be a function of the corpus callosum (and cerebral white matter) while the cerebral cortex, as resting place, is related to memory (and hence intelligence).

The corpus striatum, or as he calls it the "streaked or chamfered bodies", is concerned with sensory perception and motion; it is also his "sensorium commune". The striate body, which he first described, was for him the foremost end of the medulla. "These bodies placed between the brain . . . and its appendix . . . receive(s) the strokes of all sensible things" and are the origin also of "the first instincts of spontaneous local motions". This sounds like an anticipation of reflex activity and has been interpreted as such by Foster (1901) and Sherrington (1946). From the striatum the animal spirits or (as we would call

* Vinchon and Vié (1928) take this as meaning the autonomic system, controlled by the cerebellum which innervates heart and other viscera. If this should, in fact, have been Willis's meaning, it would be an almost visionary anticipation of the modern view of the physiology of emotion and emotional expression.

† Grünthal (1957), as others before him, has pointed out that the accessory nerve was described 100 years before Willis by Eustachio (but the illustrations were published only in 1714 by Lancisi); and that the arterial circle was anticipated 6 years before *Cerebri Anatome* by Wepfer (1658) who is best known for his post-mortem findings in patients dying from apoplexy.

‡ Foster is inclined to ascribe the important discoveries published in *Cerebri Anatome* to Willis's collaborator Richard Lower, basing this opinion on the published report of Willis's contemporary Anthony Wood (1817). Wood's opinion seems to have been biased, however. Willis paid, in the preface of *Cerebri Anatome*, a very generous tribute to Lower, and their relations seem to have been harmonious to the end (Symonds, 1955).

them now) the motor impulses, travel down to the medulla and the spinal cord from where they are carried by the nerves to the periphery.

Only *spontaneous* motor activity is associated with the striatum, involuntary motor action is allocated to the cerebellum, a distinction which, as Neuburger (1897) has pointed out, has ever since remained fundamental. Willis chose the cerebellum because he (wrongly) believed that it gave origin to the vagal and sympathetic nerves, because of its unvarying structure in all animal and human brains (in contrast to the cerebral cortex) and lastly, because he observed that in animal experiments as well as in human post-mortems lesions in posterior regions of the brain were almost invariably fatal, with disturbance of heart action and respiration. The cerebellum, as control centre of visceral activity, was later replaced by the medulla, following the experimental and pathological observations of Pourfour du Petit (1710), Lorry (1760) and Morgagni (1761). It was Legallois (1812) who finally established the existence of medullary centres as regulators of cardiac and respiratory function. Notions of cerebellar function differed widely until Flourens (1824) finally recognized it as a centre for the co-ordination of movements.

Willis's modern critics (for example, Foster (1901), Zilboorg (1941) and Mettler (1947) never tire of emphasizing the role of speculation in all these assumptions. Speculation certainly played a part; some of it was inspired, for example the localizing of animal instinct in the middle of the brain (i.e. not far from the midbrain and diencephalic centres which we today continue to relate to the mechanisms of instinctual drives). However, one cannot ignore the considerable, although primitive, observational basis for many of his hypotheses. Those that led him to the cerebellar autonomic theory have already been mentioned. In his chapter on Palsy he described a post-mortem in which the anterior cavity of the brain was filled with blood, which pressed upon one of the "streaked Bodies", thus causing motor disturbances, upon the corpus callosum with the consequence of "Hebetude and Stupefaction" and upon the optic thalamus, causing loss of eyesight. In chronic paralysis he found the striatum discoloured "like filth and dirt" and their striae obliterated.

The importance of the cerebral cortex for memory (and hence intelligence) he deduced from his comparative observations that its "folds and rollings about are far more and greater in man than in any other living creature, to wit, for the various and manifold actings of the Superior Faculties . . . Those gyrations or turnings about in four-footed beasts are fewer . . . In the lesser four-footed beasts, also in fowls and fishes, the superficies of the brain being plain and even, wants all cranelings and turnings about". Nevertheless the cerebral cortex is subordinated to the corpus callosum and cerebral white matter, for he had observed that "the Animals which excel in Memory, Imagination and Appetite . . . are furnished with a more ample Marrow". In lower animals the "cortex of the brain (may be) greater, but the medullary part very small". Comparative observation also compelled him to discount the importance of the pineal gland for the higher mental activities.

In his classification of nervous and mental disease, Willis followed the tradition of his times: chapter headings such as Mania, Melancholia, Stupidity, Palsy, Convulsions, Incubus, Hysteria, etc., are found also in the writings of Felix Plater (1602-3) who is regarded as the father of classification of mental disease, and of Montalto (1614), Sennert (1629-52) and others. Willis, however, added the first description of myasthenia gravis and, more important to our present inquiry, the first hint of dementia paralytica. In an often quoted paragraph he described cases "visited with dullness of mind and forgetfulness

and then with stupidity and foolishness, they would afterwards fall into paralysis . . . either general paralysis or hemiplegia or certain partial weakness of the limbs would ensue". Stupidity, which obviously comprehended both oligophrenia and dementia, was caused either by anatomical lesions of the cerebral white matter or by disintegration of the animal spirits. In this distinction, one may perhaps see a very early anticipation of the division between organic and functional psychoses as well as the difference between Willis's functional pathological standpoint and the "solidism" of the later morbid anatomists.

Epileptic convulsions he considered to be explosions of the animal spirits in the region of the corpus striatum, a notion which *mutatis mutandis* we meet again 200 years later in Hughlings Jackson's theory of explosive discharge of nerve cells. Hysteria and Incubus were partially assigned to the cerebellum with its control over involuntary action.

Some of Willis's basic concepts left a lasting impression: with his demarcation between voluntary and involuntary movement and their separate control centres in the brain, he has become one of the earliest architects of the autonomic system as we know it today (Neuburger, 1897; Dow, 1940). His association of control of voluntary motion with the corpus striatum was maintained—with one possible exception—until the time of Hughlings Jackson (who, in his earlier writings still accepted it) and the experimental discovery of the motor cortex by Fritsch and Hitzig (1870). It was accepted by Theophile Bonet (1679, 1700) in his book on morbid anatomy fittingly called *Sepulchretum*. In the preface to this book Willis heads the list of those to whom Bonet makes acknowledgments. Morgagni, writing 80 years later (1761), frequently refers to Willis's writings and to the *Sepulchretum*; he too accepts Willis's striatal thesis with slight modifications.* So did Caldani, in 1786, on the strength of experimental investigations. In Carpenter's 1853 edition of the *Principles of Physiology* (lately much quoted by Walshe (1957, 1958)), the striate body still controls backward movement, while the cerebellum is responsible for forward motion. Even after the discovery of Fritsch and Hitzig and their confirmation by Ferrier (1874), Meynert (1884) adhered to a subcortical highest motor centre, since he maintained the cortex was concerned only with psychic function. The exception which I mentioned concerns the work of the French surgeons and experimentalists of the 18th century who, as we shall presently see, despite their still primitive techniques, almost anticipated by 150 years the discovery of the motor cortex by Fritsch and Hitzig.

And, thirdly, Thomas Willis was among the very first to introduce the *cerebral cortex* as a substrate of important psychical function. It is strange how slowly the configuration and the functional significance of the cerebral cortex was grasped (Neuburger, 1897; Grünthal, 1957), although its intricate pattern must be almost self-evident on opening the skull. Leonardo da Vinci, a most acute observer of anatomical detail, left the convolutions a blank (Fig. 2), whereas he paid careful attention to making casts of the ventricles. Vesalius re-affirmed Erasistratus' almost 2,000 years older description of the cortical pattern as resembling coils of small intestine or cloud formation (Fig. 3), and this impression is gathered even more from some of the drawings (Fig. 4) in Descartes' *De Homine* (1662). In contrast, in *Cerebri Anatome* (Fig. 5) the drawings of the base of the brain are distinctly more realistic. They were executed by Christopher Wren, but the example of Leonardo da Vinci shows

* Morgagni also mentioned hardness of the cerebral white matter and abnormalities of the pineal gland as the chief causes of insanity.

that this advance cannot be exclusively attributed to the qualities of the artist. No further progress was made until Soemmerring (1778), a contemporary of Kant in Königsberg, Rolando (1809) and Gall and Spurzheim (1810) produced descriptions and drawings which approximate to modern macroscopic impressions of the convolitional pattern (Fig. 6). Later they were brought to even greater perfection by Leuret and Gratiolet (1839–1857) and by Retzius (1896).^{*} Increasing awareness of the functional importance of the cerebral cortex went together with improved anatomical accuracy. Gall and Spurzheim made it the seat of a plurality of mental faculties with differential localization: their teaching of Phrenology has fallen into disrepute, but not their association of speech with the frontal lobe. This—indirectly—influenced Broca (1861) and, thus Gall becomes the true initiator of cortical localization (Neuburger, 1897; Grünthal and Strauss, 1949; Jefferson, 1953; Ackerknecht, 1958).

None of the immediate successors of Willis revealed his breadth of vision, particularly in respect of cortical function. Table II shows that there were even

TABLE II
“*Sensorium Commune*”

Dura mater: Pacchioni (1701) and Baglivi (1704). Rejected by Schlichting (1750) and Lorry (1760).

Cerebro-spinal Fluid: Soemmerring (1796).

Corpus callosum or cerebral white matter: Vieussens (1684); Boerhaave (1708); Lancisi (1739); La Peyronie (1741); Hartley (1749); Albrecht von Haller (1757–66); Burdach (1819–26).

Basal ganglia: Corpus striatum (Willis, 1664). Thalamus and “sensory ganglia”, “automatic apparatus” (Carpenter, 1853).

Medulla: Andrew Harper (1789); Chiarugi (1793); Rolando (1809); Thomas Laycock (1860) and others.

near-relapses into scholastic views. With Pacchioni (1701) and Baglivi (1704) originated the hypothesis that the dura mater was the most important part of the body, the motor of the movement seen in the exposed brain. It held sway until the role of respiration in this apparent movement was demonstrated (Schlichting, 1750; Lorry, 1760). Soemmerring (1796) designated the cerebro-spinal fluid as the “organ of the soul”. The discrepancy between Soemmerring, the careful neuro-anatomist, and the writer of the “organ of the soul” is explained by the current belief at that time that the cerebral cortex was compounded of glands, a belief which goes back to Malpighi (1669), the discoverer of capillaries and an early, no less successful, pioneer microscopist of the nervous system.

Among the many who attached significance to the cerebral white matter we notice (in Table II) Boerhaave (1708) and La Peyronie (1741) one of the French surgeons for whom the corpus callosum was “le siège de l’âme”. Albrecht von Haller (1757–1766) also found the cerebral cortex (and its membranes) unresponsive and, therefore, functionally unimportant. Responses to irritation were only obtained by thrusting a needle deep into the white matter. In general, however, he was against any appreciable focal localization in the brain, and many of Willis’s (and others’) earlier achievements were lost through his and his disciples’ negative attitude.

^{*} For further detail and illustrations *vide* Grünthal (1957).

The "sensorium commune" of Carpenter (1853) was located in what he called the "automatic apparatus" which he based on the thalamus and "sensory ganglia" such as the olfactory bulbs, corpora quadrigemina, auditory and gustatory ganglia in the medulla. The cerebral cortex, however, provided "unconscious cerebration". Consciousness and memory were functions of the automatic apparatus.

Some writers even went back to the medulla as the "common sensory". Among these, as late as 1860, Thomas Laycock regarded cerebral and cerebellar hemispheres merely as extensive peripheries; and even Rolando (1809) maintained his medullary sensorium commune despite his experimental discovery of the deleterious effect of destruction of the cerebral hemispheres upon higher mental function. Perhaps the most drastic supporter of the medulla was Andrew Harper (1789), who persisted on how effectually the sensorium commune or "prime movement is secured by the cortical and cineritious part of the brain" almost disparagingly dismissing the "intermediate meanders, circumvolutions and reticulations which constitute the glandular part".* Harper was one of the writers of treatises on psychiatry which were characteristic of the 18th century, particularly its second half, and which included in this country the monographs published by Battie (1758), Perfect (1787), Cullen (1781), John Brown (1780), Crichton (1798) and Cox (1806). Although most of these writers maintained—in varying degree—that mental disturbances are largely caused by lesions or disturbances of the brain and its membranes, they added few observational data. Often the pathology was confined to enumeration of "causes" such as bony abnormalities, insolation, inflammation and—above all—congestion of meningeal and cerebral blood vessels which was widely held to be an important pathogenic factor in insanity. A vascular factor was suggested by enlargement and ossification of cerebral arteries (clearly alluding to arteriosclerosis) which had already been mentioned, among others, by Willis, and was also stressed by Harper, Crichton and Andrew Marshal (1815).

No systematic investigations of the pathology of insanity appeared much before the end of the 18th and the beginning of the 19th century: then came contributions by Greding (1781, 1790), a German psychiatrist, whose work was translated by Crichton in abbreviated form; Haslam (1798); Crowther (1811), and Andrew Marshal (1815). Although the detail of their macroscopic pathological observations is now only of historical interest,† it

* That Harper did not deny the existence of a pathology of these "glandular parts" becomes clear from the following passage: "From all these discussions, it appears to me, at least, abundantly evident that no general, partial, particular affection, praeternatural appearance or morbid change, cognizable to the senses, within the brain, nor any stimulant, irritative or debilitating cause in the circulatory system, can possibly be capable of inducing or predisposing to insanity . . . it has been closely demonstrated that Insanity is a disease of the mind independent of any corporal exciting cause" and he concludes (p. 29) ". . . the proximate cause and specific existence of Insanity to be a positive, immediate discord, in the intrinsic motions and operations of the mental faculty . . . its exact seat to be the prime movement".

† Greding reported macroscopic findings in 216 cases of insanity, including mania, melancholia, idiocy and epilepsy. He paid attention to size and thickness of skull, to venous sinuses, meninges, ventricles, cerebral cortex and white matter, cerebellum, pituitary, pineal gland, etc. The one or other abnormality was present in every case, but the only consistent change appears to have been a tendency to softness in the cerebrum, and to hardness in the pituitary. The findings in the visceral organs were not significant. Few insane people died suddenly or in convulsions, and there was no close relation between insanity and gout, rheumatism or other painful disorder.

Somewhat similar post-mortem investigations (though on smaller material) were reported by Haslam and by Marshal, the latter attributing the pathological changes in the nervous system to alterations of blood supply. Crowther's opinion on the causal significance of the post-mortem findings is, on the whole, critical; his argument is somewhat reminiscent of that of Harper.

is important to record that these investigators (with the exception of Crowther) were convinced that insanity was always associated with anatomical changes in the brain. The strongest expression of this belief has been given by Haslam who asserted "that madness has always been connected with disease of the brain and its membranes", and is revealed post-mortem in every case of an unselected variety of mental patients, and without exception. It is also interesting to note that—with Greding, Haslam and Marshal—somatic pathology had become morbid anatomy. This was in keeping with the transition from humoral pathology to "solidism" which took place during the closing period of the 18th century, mainly as a consequence of Morgagni's assault upon humoral pathology.

Haslam* is credited with the first clinical description of dementia paralytica—his case 15. However, from the point of view of pathology, this case differed from the others only in greater quantity of cerebrospinal fluid. While, in the words of Tuke (1882) Haslam "may seem to have stumbled upon G.P.I.", it is the great merit of Bayle (1826) and Calm  il (1826), both disciples of Esquirol, that they laid the basis for dementia paralytica as a clinico-pathological entity. That their results were obtained without the aid of the microscope underlines the magnitude of their achievement. Ackerknecht (1959) rightly points out that about a third of the inmates of a mental hospital suffered from the disease at that time. If other syphilitic conditions, encephalitis, senile and arteriosclerotic psychoses and oligophrenias are added, this figure may easily have reached or even surpassed 50 per cent. The temptation to look for similar changes in the remaining cases must have been great, the more so as the range of the normal at that time was ill-defined.

The dogma of invariable anatomical changes in the brains of the insane took a firmer and more enduring hold in Germany than in other countries. This was due partly to the influence of their own "somaticist" school, but also to the influence of British and French organic trends. The sudden rise of neurohistology in the 1830s must have acted as a considerable stimulus: within a few years major discoveries were made by Ehrenberg (1836), who was the first to demonstrate a nerve cell under the microscope; Purkinje, Valentin, Schleiden, Schwann, Robert Remak, von K  lliker and others (Fig. 7). Upon this basis Rudolf Virchow was soon to build his *Cellularpathologie* (1858), and although he was not much concerned with the psychiatric aspects, he acted as a powerful support for others, of whom the most important were Griesinger, Schroeder van der Kolk and Meynert. Of these, Schroeder van der Kolk, of Utrecht (1863, publishing in German), was perhaps the most dogmatic. He never failed to discover pathological changes in cases of mental disease: in the frontal cortex, when intellectual deterioration had been present; and in the upper and hind lobes in melancholic patients.

Griesinger (1845, 1861, 1867) repeatedly re-affirmed that for him the true answer to the problem of insanity would be given by cerebral and, in particular, cortical morbid anatomy. He admits, however, that a classification of mental diseases according to their nature—that is, according to the anatomical changes of the brain—was at that time not possible. Dividing the psychoses into two large groups: one of emotions and emotional states, the other of false modes of thought and will, he continues: "pathological anatomy shows, even at present,

* Haslam made other contributions to psychiatry of which Leigh (1955) has given a sympathetic account. This author also mentions that Pinel, customarily "somewhat sarcastic in his references to England . . . clearly has a considerable respect for Haslam".

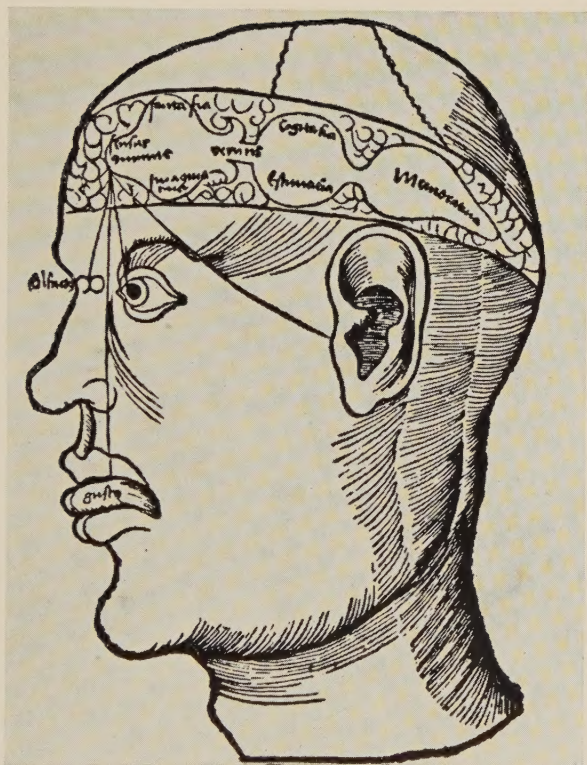


FIG. 1.—Diagram of the ventricles of the brain, from G. Reisch, *Margarita philosophiae* (reproduced, with the author's kind permission, from Charles Singer *A Short History of Anatomy and Physiology . . .* ", New York and London, 1957). The inscriptions (from left to right) are as follows:

Sensus communis	fantasia	vermis	cogitativa	memorativa
	imaginativa		estimativa	

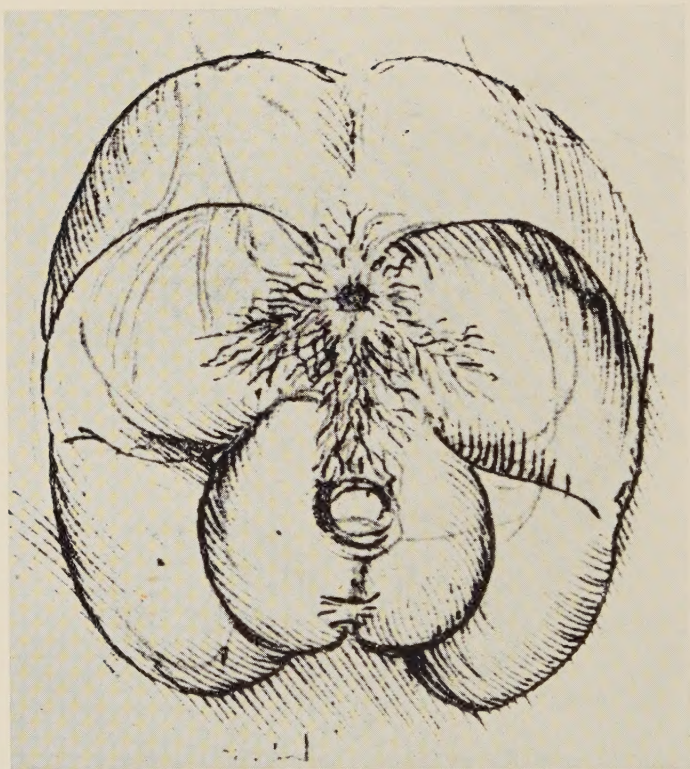


FIG. 2.—Base of brain (reproduced from Leonardo da Vinci, *Quaderni d'Anatomia*, Vol. V, part of folio 7).

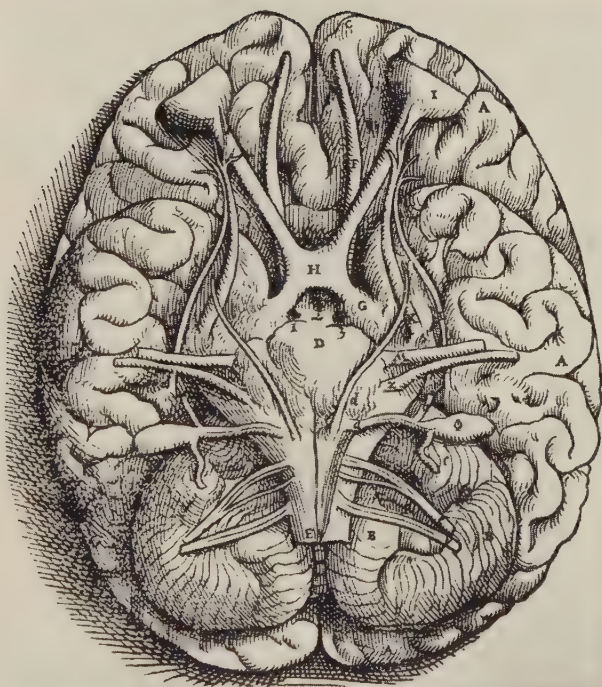


FIG. 3.—Base of brain (reproduced, with the librarian's kind permission and help, from the original edition of Vesalius' *De Fabrica Humani Corporis*, 1543, in the Wellcome Historical Medical Library, London).

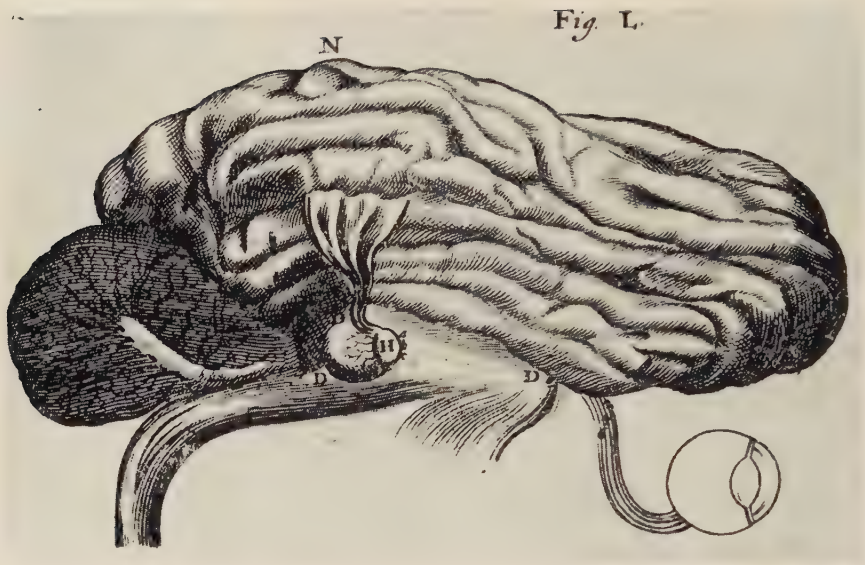


FIG. 4.—Sagittal view of brain (from Descartes' *De Homine*, 1662).



FIG. 5.—Base of brain (from Th. Willis' *Cerebri Anatome*, 1664. Drawing by Christopher Wren).



FIG. 6.—Base of brain (from Gall and Spurzheim *Anatomie et Physiologie du Système Nerveux*, I, 1810).

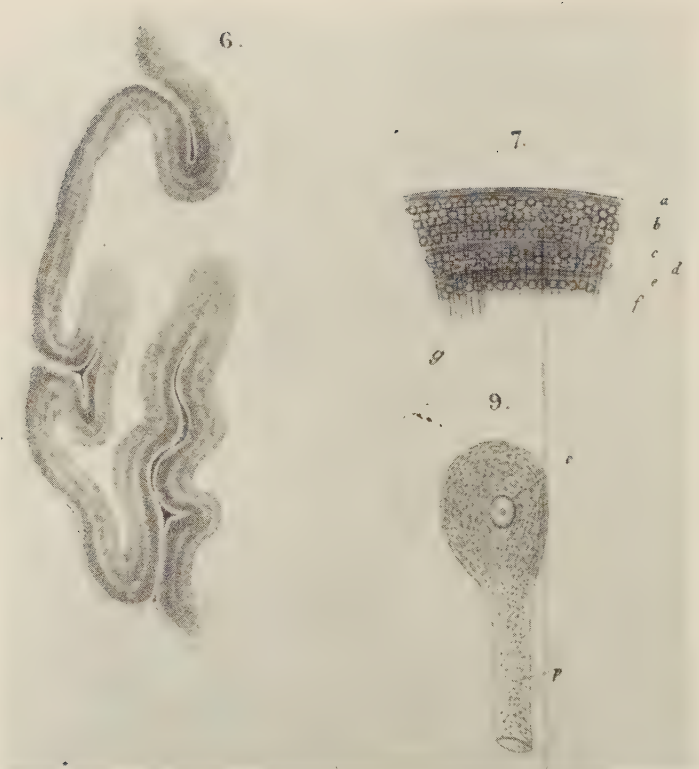


FIG. 7.—From R. Remak, 1844. Part of Table 12, showing (in Fig. 7) a diagram of the six-layered cerebral cortex.

that in the first group, or in the initial stages of insanity, it is rare to find important organic alterations . . . whilst in the second group . . . very often exist palpable organic alterations . . . particularly atrophy of the brain, more or less extensive, with oedema of the membranes and chronic hydrocephalus. Here, also is to be found the basis of a true diagnosis, that is anatomical diagnosis (1867, p. 207).

Theodor Meynert (1867, 1884, 1890) showed an even greater anatomical bias. He was so convinced that cerebral anatomy would solve the problem of mental disease that he objected even to the use of the term "psychiatry" (Zilboorg), which for him was synonymous with cerebral anatomy. In his general scheme of the brain, he considers that all afferent sensory fibres terminate in basal or subcortical centres which are also the starting point of descending motor tracts. For example, the fibres of the optic tract, he thought, ended in the grey matter of the superior corpora quadrigemina. The cerebral cortex is a completely independent "organ"; it is in connection with the subcortical motor and sensory centres, but all impulses that reach it have lost their material "sensual" character and have become "images"; their intricate association through the arcuate fibres builds up consciousness and the ego. Civilized behaviour develops through the effect of inhibitory cortical impulses upon the lower subcortical centres. The surface position of the cerebral cortex favours its wide encompassing (umgreifende) function. The cortex, though concerned exclusively with psychic phenomena, is not uniform in structure. It is rather a complex of "organs", and certain structural differences, e.g. the hippocampus and the medial occipital cortex (the large nerve cells there bear the name of Meynert) suggest also differences of function. Although the discoveries of Hitzig and Fritsch, Jackson, Ferrier and others were known to Meynert, they did not impinge upon his view of the exclusive psychic function of the cerebral cortex: only psychomotor phenomena, "psychical" deafness and "psychical" blindness could be of cortical origin. Such was Meynert's authority that Hitzig (1900) in his Jacksonian lecture in London seems to have accepted the "psychomotor" nature of the cortical motor phenomena which he together with Fritsch had charted.

According to Meynert cerebral function and, in particular, the complex processes of cortical association are accompanied by hyperaemia. Normally the extent of this "Funktionshyperaemie" is limited, since the brain and its cortical surface are enclosed within a rigid bony capsule and generalized hyperaemia would therefore inevitably result in oedema and swelling of the brain and, thus, produce abnormal mental and neurological phenomena. The opposite, lack of nutrition, would also result in mental and/or bodily disease and, if lasting, would give rise to anatomical damage in the brain.

On the basis of this general concept of brain function, Meynert attempts a classification of mental disease. Mania and melancholia are diseases due to cortical irritation. All hallucinations are due to abnormal subcortical function. Hypochondria, hysteria, neurasthenia and epilepsy (apart from the localized cortical Jacksonian type) are subcortical or bulbar phenomena. Epileptic seizures are conceived of as being caused by vasomotor constriction of arteries at the base of the brain and this concept is extended to the transient hysterical paralyses and sensory disturbances which—interestingly—are attributed to spasm of the thin-walled and recurrent anterior choroidal artery. Paranoia he thought was caused by an irreversible anatomical lesion, possibly manifesting itself as general atrophy of the brain.

The views of Griesinger and Meynert, as well as of Maudsley and other "system builders", have been criticized by Zilboorg for their materialist tendencies. Aubrey Lewis (1951) has already corrected this statement as erroneous, in so far as Maudsley was concerned. Neither Griesinger nor Meynert were materialists, though naturally they expressed their views in the language of associational psychology which was the widely accepted contemporary theory. Both repeatedly and emphatically stressed that the relationship between mind and matter remained mysterious. Both more or less adhered to the philosophies of Herbart, Fechner and Lotze, whom they frequently quote. These were predominantly idealistic, following in the wake of the great German idealist systems of the first half of the nineteenth century. If such superficial analogies are of any avail, one may compare Meynert's concept of brain function, in its aesthetic simplicity with that of Plato, as outlined in *Timeo* (Magoun, 1958). In Plato's view the divine part of the soul was localized in the spherical marrow of the cranial cavity which resembled in shape the Earth and the Universe, while the mortal portions inhabited the vertebral canal and spinal cord, just as Meynert's hemispherical cortex, which was responsible for all higher mental function, "encompassed" the subcortical regions which were concerned with lower and peripheral function.

Meynert's teaching inspired, among others, Flechsig, Wernicke, Forel and Freud (the neurologist), and through Wernicke and his school it has maintained some of its momentum into the present time. On the other hand, the reaction against the almost exclusively anatomical bias underlying the "systems" of Griesinger, Meynert and others was also considerable. Maudsley (1867), for instance, politely but definitely rejected Schroeder van der Kolk's claim that morbid anatomical changes may be detected at the autopsy of all cases of mental disease. To him "it is beyond doubt that important molecular or chemical changes may take place in those inner recesses to which we have not yet gained access". He also draws attention to the researches of Du Bois Reymond and others who "have shown that there are currents of electricity engendered in nerve". Ferrier's (1878) indictment that "morbid anatomy (is) far from being co-extensive with pathology" and that "deep mental abnormalities leave no trace discoverable by dissection and even the most advanced investigation" is equally incisive. In Germany, the reaction also gathered momentum. Oscar Vogt (Lewey, 1953) relates how on a visit to Kraepelin in 1894 he found him full of doubt about the value of anatomical research in mental disease (a judgment which he modified ten years later, impressed by the work of Nissl and Brodmann). The term "brain mythology" came to be used increasingly against, in particular, Meynert's trends of thought. Interestingly the phrase had been coined by Nissl (Bumke, 1925) who, in turn, was soon to embark together with Alzheimer and with collaborators from many lands upon the pathological anatomy of the psychoses.

In retrospect, it is now clear that their principal achievement in the field of psychiatry was the histopathology of the dementias: diffuse or widely disseminated degeneration, followed by disappearance of the neurones in the cerebral cortex and white matter invariably resulted in intellectual deterioration, or in early life, arrest of intellectual development; no matter whether the nature of the brain process was inflammatory, vascular, anoxic or due to malformation, trauma, nutritional deficiency, abiotrophy or senility. In the early days the list also included dementia praecox, but although powerful claims are still presented in our days, they have not been generally accepted. Today th

most comprehensive investigations have been conducted by the Vogt's (1952) and their disciples. The histological cell changes which they report in many cortical and subcortical areas of schizophrenic patients are not, however, specific and it is not easy to differentiate them from the normal range. It is the conviction of many workers including myself (1952) that more sensitive methods will be required to determine their significance.

Notwithstanding this limitation the achievement of morbid anatomy in the field of the dementias was formidable: it remains one of the solid pillars upon which psychiatric diagnosis and teaching rests. I cannot agree with Ackerknecht (1958) that "histology has not yielded any final answers or practical results for psychiatry and, in this, has been largely unimportant and even worthless" (although he acknowledges the "scientific" value of the work). This sweeping statement in an otherwise so objective historical treatise, hardly does justice to the many practising psychiatrists, from the times of Greding, Haslam, Esquirol, Meynert, Hitzig, Flechsig, von Gudden, Nissl, Alzheimer to Adolf Meyer, who carried out work in neuro-anatomy and neuropathology in order to unravel some of the secrets of mental disease. The psychiatrist is too often inclined to disown such achievements and to credit them to neurology or to any other branch of medicine. In fact, as this review shows, neuropathological investigations were initiated, and—to a large extent—developed in psychiatric institutions. Behind this attitude hides a curious "purist" assumption that problems of the mind require special methods for their solution, something akin to the approach which we have already encountered in Harper's argument. One wonders what will happen to the schizophrenias and the other functional psychoses: will they also be disowned by the psychiatrist once biochemistry or any other science has provided what is likely to be—at least partially—a physical substrate?

The search for a somatic basis for the functional psychoses has been a central task of pathology in the recent past. Since intellectual deterioration is not a primary sign of these psychoses, which display their abnormalities rather in the emotional sphere of the personality, attention has understandably tended to shift from the cortex to subcortical regions. This shift of interest was precipitated by the exciting new knowledge of extrapyramidal syndromes in the first two decades of this century, and by the dramatic natural experiment of lethargic encephalitis, with its symptoms of hypersomnia, loss of initiative, psychopathy-like behaviour, and of hallucinatory and compulsive phenomena in the course of oculogyric crises, which were all encountered as sequelae of circumscribed lesions of the grey matter surrounding the third ventricle and aqueduct. The area which has been submitted to the most intense scrutiny by pathologists as well as by experimental physiologists and biochemists, roughly comprehends the hypothalamus, closely linked through the pituitary gland to the endocrine system, the thalamus and thalamo-frontal radiation, the pre-frontal region and the so-called rhinencephalon. Time prevents me from adequately describing the successive stages of this research, nor is such a description necessary, since the work is still fresh in our minds. I should, however, like to say a few words about the frontal lobe.

Since the crow-bar case described by Harlow in 1848, and subsequent descriptions by Ferrier (1878), Welt (1887) and many others, it has been known that bilateral lesions of the prefrontal region may cause changes in the personality and, in particular, in the affective sphere. A considerable landmark in the evolution of the frontal lobe syndrome were the careful experimental

investigations which Bianchi (1920) carried out from about 1895 onwards. In a polemic which has become famous, Bianchi defended the function of the prefrontal lobes as seat of intellectual and emotional synthesis against Emil Flechsig's (1896) thesis, that the parieto-temporo-occipital association zone is the most important region for human mental activity. As it turned out, both were right: Flechsig, in stressing the importance of this zone for the symbolic tools of intelligence: language, praxis, gnosis, and memory, while the frontal region is increasingly recognized as being concerned with the consciousness of the self (Freeman and Watts) and ego function. In the chart which was the outcome of Karl Kleist's (1934, 1937) clinico-anatomical experiences of head injuries in the first world war, the personal ego is associated with the orbital region, while the corporeal (visceral) ego is brought into connection with the cingular region. Although one cannot accept Kleist's pin point localization of mental faculties, this conception of the association of frontal and cingular regions with ego function was, in the words of Freeman and Watts, an act of "penetrating insight" which profoundly affected all subsequent discussion.

With the advent of prefrontal leucotomy and of selective blind, open or stereotaxic interventions, and with the subsequent introduction of temporal lobectomy in cases of temporal lobe epilepsy, the frontal (and temporal) lobes have become of practical concern in psychiatry. I will not here consider the therapeutic value of these surgical interventions. Indications for frontal lobe surgery have in the recent past become much more restricted, and, in many conditions, its place has been taken by chemotherapy, which may eventually supersede it. The impact which neurosurgery has made in mental disease is deeper than the therapeutic issue alone: the neurosurgeon, during the therapeutic intervention, acts almost as a neurophysiologist, making important observations which often amount to a physiological experiment. Jefferson (in his Stephen Paget lecture (1955)), has dwelt on the ethics of man as an experimental animal, pointing out that in certain investigations man is the most suitable, and whenever higher nervous and mental activities are involved the only animal from which experimental observations of a basic physiological nature may be obtained. He urged that this fact imposes a special responsibility on the neurosurgeon and his collaborators. Animal experimentation does not, however, diminish in importance. It usually precedes the "experimental" procedures in the human brain and always supplements them. Jacobsen's (1935) frontal lobectomies in chimpanzees probably hastened the introduction of prefrontal leucotomy by Moniz (1936); but without the maturation of modern neurosurgical techniques, this type of brain experimentation would not have been possible.

The present situation has much which recalls the brain surgery of France in the 18th century. At that time burr holes were made in cases of contrecoup and this intervention became fashionable and was applied to a great variety of conditions. Eventually the fashion petered out, but it left its important landmarks: not only was La Peyronie (1741) able to study the significance of lesions in the white cerebral matter for mental function, but, more important still, Pourfour du Petit (1710) established the relationship of the pyramidal tract to motor function, described its crossing and, tentatively at least, associated *incomplete* paralysis of the extremities with malfunction of the opposite parietal cortex. He and his followers were early pioneers of the motor cortex (Neuburger), although they did not grasp the full significance of their findings,

and continued to implicate the striatum as the principal control centre of movement.

The neurosurgeon of today has at his disposal techniques which are infinitely superior, and he is also powerfully aided by the electrophysiologist who, in turn, is able to supply him with methods of electrical stimulation and action potential recording which in accuracy attain almost to microscopic levels; he is aided also clinically by a far more advanced neurology, psychiatry and psychology. It is, perhaps, too early yet to assess the permanent gains in knowledge we may have reached from the present neurosurgical era, but it is permissible to say that it has led to a far clearer understanding both of frontal lobe function in its relation to the sphere of the ego, and of temporal lobe function, with its role, in Penfield's (1958) view, in recall and interpretation of past experience. Thalamus and hypothalamus with their adjacent regions are being explored by direct stereotaxic interventions in animals and in man, and the recent operations for extrapyramidal disease are adding other centres to this list: hypophysectomy, now often practised in cases of carcinoma, is providing opportunities for studying anew the complex cerebro-hypophyseal connections, in man, and the sites and pathways of hormonal secretion. The carrying-out of temporal lobectomy in cases of temporal lobe epilepsy has provided interesting new information on the centres in the infero-medial temporal region—Ammon's Horn, uncus and amygdaloid complex, and their manifold connections.

The functional concept of the "visceral brain" or "limbic lobe" is perhaps one of the most interesting crystallizations of this new experimental approach. It has been slowly emerging during the last three decades, beginning with Cannon's (1915) and Bard's (1928) experimental investigations and with Kleist's experiences in head injuries. It acquired its basic form, when Papez (1937) presented his "proposed mechanism of emotion and emotional expression" linking mammillary body, anterior thalamic nuclei and the cingular region with the hippocampus. Maclean (1949) added posterior orbital cortex, temporal pole, insula, amygdala and other areas between frontal and temporal cortex. Much of the evidence concerning "visceral" activities remains controversial and it seems that speculation has outstripped the available facts. The same may be said about "the ascending reticular formation", another interesting crystallization of recent experimental work and observations in man. Its location in brain stem, hypo- and subthalamus, intralaminar and reticular thalamic nuclei is—so far—only approximate, and despite recent anatomical studies (Olszewski, 1954; Nauta *et al.*, 1954, 1958; Papez, 1956; Brodal, 1957), the anatomical pathways are not yet fully elucidated. It seems to the present writer that much that previously had been conceived of as hypothalamic activation of the cerebral cortex (and which was based upon solid experimental and clinico-pathological experience) has been somewhat summarily incorporated into this new "formation" which is probably composed of several relatively independent relay-systems. Of these the pontine and midbrain relay may be identical with the ascending pathways linking the medullary centres with the hypothalamus, from which in turn, fibres connect with the thalamus.

It is important that this large hypothetical element in these useful concepts is well understood. Perhaps they have become too much like household words, ready on occasion to be introduced like the "deus ex machina" of the ancient theatre. We no longer think now in terms of the "sensorium commune", and the phrase "brain mythology" refers, as we have seen, to a specific period of

the closing 19th century. We have yet to learn that no generation is quite immune to the dangers of either.

The *biochemist* is the latest arrival in the field of the pathology of mental diseases. Although since the days of iatrochemistry chemists have concerned themselves with the phenomena of mental abnormality,* it was not until our own time that the biochemist—with infinitely matured techniques and knowledge, has undertaken in earnest to grapple with the problems of psychiatry and neurology. Fabing (1958) has tabulated important avenues of biochemical research which are at present in progress, and Gould (1959) has supplemented these with a review on research into the field of hormones and nutritional deficiency. The very diversity of the approaches indicates that this whole province is in an experimental stage. The neurohormones and their derivatives, among them serotonin and adrenochrome, have been foremost in the limelight, because of their pharmacological resemblance with or antagonism to mescal and lysergic acid. Theories have been propounded—though at the moment not yet verified—as to their possible pathogenic role in schizophrenia and kindred psychoses.

I do not believe that this promising biochemical outlook will replace the older morphologically orientated approaches. Biochemists (Waelsch, 1957), have recently become very much aware of the complexity of the brain, and of the possibility of a focal disturbance underlying psychotic manifestations. Gjessing (1938) always postulated that an abnormality in or near the hypothalamus may be at the root of nitrogen retention in periodic catatonia. Feldberg and Sherwood (1955) in their intraventricular experiments with neurohormones, and other substances, were also led to believe that the main action was on the grey matter surrounding the 3rd ventricle and aqueduct. This tallies with the well-known occurrence of manic syndromes and stupor after hypothalamic lesions in man. Although these organic syndromes may not be fully comparable with corresponding states in the functional psychoses, they clearly represent interesting pointers to the site of abnormal function.†

It is also noteworthy that the quantity of neurohormones (sympathin, serotonin, substance P) is greatest in the diencephalon and the tectal areas of the midbrain (M. Vogt, 1954; Amin *et al.*, 1954); and Holzbauer and Vogt (1956) have in addition reported reduced values of sympathin after injection of reserpine.

All this points to the possibility of a localized pathology for some of the psychoses, and, hence, the anatomical histological approach is likely to retain an important place. Histology itself, however, is at present under the tremendous impact of recent advances in biochemistry and biophysics, and its future contributions are likely to be made not so much by its traditional methods as by new histochemical, microchemical and ultramicroscopic techniques.

ENVOY

This brings me to the end of our journey. It is clearly not possible to give a summary, as the whole of this lecture is a summary report on developments

* For developments during the 19th century McIlwain (1958) should be consulted.

† Mayer-Gross (1959) has discussed the possibility that the frequent synaesthetic phenomena in the so-called model psychoses may depend on abnormalities in the reticular formation. Another interesting aspect of the problem has been raised by Baldwin *et al.* (1959) who have shown that the response of chimpanzees to lysergic acid is abolished by previous (bilateral) ablation of the lateral temporal convolutions (but not by that of the prefrontal cortex). Their results not only underline the importance of the temporal cortex to perceptual representation, but also point to a focal pathology of the manifestations caused by "hallucinogenic" drugs.

over a vast period of time. I am painfully conscious of its many omissions and other shortcomings, some of which were dictated by the time limit of the lecture. Much sustained effort will be required before a history of neuropathology in relation to mental disease can be written. Furthermore, for the sake of clarity, I have had to concentrate upon a main theme; other important ramifications (and names) have had to be suppressed.

Although among the builders of neuropathology we find distinguished workers of many lands, it may have come as a surprise to some who are cognizant only of the later stages, to realize how considerable the British share has been. We have the authority of J. B. Friedreich, one of the German somaticists of the early 19th century, that the organic point of view had been learned from the English. We have met Haslam and Andrew Marshal who were among the earliest to carry out systematic pathological examinations of the brains of mental patients. They generalized their findings too much, which was excusable at the time, and they identified pathology with morbid anatomy—a mistake of even greater consequence, as we have seen. Among the earlier critics of this “solidism” are Maudsley and Ferrier. I entirely agree with Aubrey Lewis’ relevant passages in his enlightened portrait of Maudsley, in the Maudsley Lecture of 1950. Maudsley’s criticism has an almost modern ring; the shift of emphasis in present-day psychiatry towards genetic, biochemical and neuro-physiological research would have caused him no surprise: what greater homage could be paid to the man whose name is remembered in this series of lectures! Sir Aubrey compared Maudsley with Kraepelin—and this is correct as far as their position in clinical psychiatry in their respective countries is concerned. Chronologically Meynert would have been a closer comparison: both men published major and characteristic treatises in the same year, 1867. What a difference between the sober realism of Maudsley and the lofty, but quickly-dating hypotheses of Meynert! Maudsley, of course, was not an anatomist, nor was he practising any other ancillary science, while Meynert has a considerable number of anatomical discoveries to his credit, and he must be regarded as the founder of cytoarchitectonics, which had its remarkable achievements but, in its excesses, has not quite shed its romantic origin.

At the beginning of the modern era we met the towering figure of Thomas Willis. In this country his fame rests more on the arterial circle which bears his name and the description of cranial nerves and of myasthenia gravis, than on his basic contributions to the understanding of cerebral function. Only in recent years has he been rightly acclaimed as the father of comparative neurology (Dow, 1940), and of the autonomic nervous system (Sheehan, 1936). It was in the main left to Frenchmen to emphasize his important place in the development of neuropsychiatry: to Calmeil (1845), himself a pioneer in the field, who considered that what Thomas Willis had to say amounted almost to a complete treatise on cerebral pathology; to Soury (1899), who praised Willis’s wide perspectives, his truly ingenious penetration of the phenomena of life and his depth and sweep of language recalling that of Shakespeare; and lastly to Vinchon and Vié (1928) who hailed him as a “*maître de neuropsychiatrie*”. Modern opinion has been somewhat biased by Foster, who over-emphasized what was time-bound in Willis and probably unduly (Symonds) minimized Willis’s anatomical merits in favour of his associate Richard Lower. Zilboorg also made severe strictures on the work of Willis, who (he said) laid “the foundation of a psychiatry without psychology which . . . while rendering inestimable service to neuro-anatomy, neurophysiology, and neuropathology

almost totally discarded the study of the very psychological phenomena which these men seem to have set out to study". Zilboorg was anxious to trace a line of development from Weyer, Stahl, Pinel, to the modern psychopathology of Freud, in which naturally Willis would not have a place. But surely, both the organic and psychological approaches are indispensable for the understanding of mental disease and should be pursued side by side.

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SOME PROBLEMS IN THE STUDY OF PSYCHOTIC ILLNESS*

By

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I am deeply appreciative of the great honour you have done me in electing me as your President for the coming session. Although very sensible of this honour I am also much aware of my own shortcomings when I remember the distinguished men who have preceded me in this office. The following contribution, I am afraid, contains very little that is original. The purpose of this paper is rather to emphasize a point of view in the study of psychotic illness, which does not always seem to receive adequate attention.

It is only in recent years that some medical schools and universities have had the opportunity of carrying out investigations on psychotic patients by reason of the fact that in some instances they have acquired in-patient departments or have worked in conjunction with mental hospitals. The history of the development of research, especially scientific research, in the psychoses in this country is an interesting one. In the last three decades of the nineteenth century and up to the outbreak of the first world war there were, in addition to the Bethlem Royal Hospital, two outstanding psychiatric institutions where psychiatrists with a sincere interest in their specialty would invariably receive their training, apart from going abroad. They were, of course, the West Riding Asylum, Wakefield (now Stanley Royd Hospital), and the Royal Edinburgh Asylum. In the universities and medical schools generally, little or no interest was taken in the subject, the clinical practice of the specialty being largely carried out by neurologists.

You are all very familiar with the history of the Bethlem Royal, and with the limited time at my disposal I only propose to give the briefest details of other hospitals in so far as they have a bearing on this paper. Firstly, with regard to Wakefield, this hospital was opened in 1818, having been built on the lines suggested by Mr. Samuel Tuke of The Retreat. Its first Medical Director, Sir William Ellis, later became Superintendent of Hanwell Asylum in 1831. During the time of the next three Medical Directors, Drs. Corsellis, Alderson and Cleaton, there were no noteworthy developments, but it was during this period from 1857-58 that Dr. Henry Maudsley was on the staff of Wakefield Asylum as a temporary house surgeon, and apparently even during that short period made a great impression. He was awarded a testimonial by the Committee in which they expressed great admiration for his ability.

From the point of view of research the most important phase in the history of Wakefield Asylum started with the appointment of Dr. J. C. Browne (later Sir James Crichton Browne) as Superintendent in 1866. One of the unsuccessful applicants for the post at that time was Dr. T. S. (later the famous

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Sir Thomas) Clouston. It was during Crichton Browne's ten years of office that Wakefield began to acquire European fame. Indeed it may be said that he, Crichton Browne, was the first ever to pursue scientific research in mental diseases in this country. At that time it must be remembered that as far as the organic field was concerned there was no bacteriology or biochemistry, and physiology was only rudimentary. Crichton Browne naturally therefore concentrated on morbid anatomy and pathology, and on attempting to correlate clinical manifestations of mental disease with abnormalities in this field. He was responsible for the opening of the famous Pathological Laboratory and for the appointment of the first pathologist, Dr. T. W. McDowall. In his Annual Report to his Committee in 1872 Crichton Browne writes: "The appointment of a pathologist which you have thus sanctioned is, I believe, a somewhat momentous step in the march of scientific progress in the lunatic asylums of this country. As far as I am aware, no other asylum is yet provided with such an officer." (In fact he was 20 years ahead of other institutions.) Crichton Browne not only fostered research in this hospital but also kept his medical staff up to date by inviting prominent lecturers and doctors to hold discussions at the hospital. In this way he was undoubtedly able to create a milieu which fostered a spirit of enquiry, and helped to maintain the medical work at Wakefield on a high plane. A few words about this remarkable man might not be out of place. During his medical education he was a pupil of Lister and also studied at the University of Paris. His medical career started in 1861 and he was medical officer successively in Devon, Derby and Warwick Asylums. As stated, in 1866 he became Director of Wakefield where his clinical and pathological investigations paved the way for the later researches of some of our greatest neurologists. In 1876 he was appointed a Lord Chancellor's Visitor in Lunacy, a post he held until 1922. This may seem a very strange promotion but by then he had already made a name for himself, and in 1878 he was President of the Medico-Psychological Association. In 1883 at the proposal of Charles Darwin, he was elected a Fellow of the Royal Society. He was given numerous honorary degrees and was one of the founders of that famous journal *Brain* which he edited for a time with Hughlings Jackson and David Ferrier. He had a large number of interests and his literary output was prolific even in advancing years. He was a gifted orator and his writings bear the imprint of accurate thought and clear expression and of considerable literary ability. He gave the first annual Maudsley Lecture in 1920. I was privileged to see him once at an R.M.P.A. meeting in 1934 or 35. His Dundreary whiskers and Victorian garb, together with his erect bearing even when he was well over 90, was a sight never to be forgotten.

It is beyond the scope of this address to enumerate all the famous men who passed through Wakefield Asylum in the next 30 to 40 years, but it is perhaps not always remembered that the late Sir David Ferrier was one of the earlier workers in the Wakefield laboratory and here carried out in 1873 his epoch-making experimental researches on the localization of cerebral function. From 1872 to 1915 no less than 23 pathologists received their training at Wakefield, among whom figured Edwin Goodall in 1890-91. In 1876 Crichton Browne left and was succeeded by Herbert Major as Director. He had already been in the service of the hospital since 1871. He had apparently acquired a considerable reputation by his histological researches in conjunction with William Bevan Lewis, who was appointed the fourth pathologist in 1876. It is interesting to note that during his period of office reference is made to his lectures on mental diseases at the Leeds School of Medicine. Bevan Lewis

succeeded as Director in 1884; he acquired a greater scientific reputation than any of his predecessors or successors at Wakefield for his extensive, painstaking, accurate and detailed description of the neuropathology and neurohistology of the various forms of psychosis. In this field Bevan Lewis was a leading exponent, whether in this country or abroad. He devised a method of staining frozen sections of cortex with a British dye, aniline blue-black, which was superior to any the Germans had manufactured, and he demonstrated what he called the "scavenger" cells, now known as astrocytes. The lipoid inclusion bodies were regarded as the remains of phagocytosed degenerated nerve cells. There is no doubt that Bevan Lewis can be regarded as a pioneer in this field. Much preliminary work was done showing certain changes in acute psychoses, and others in chronic dementias. Whether all these changes were secondary, due to intercurrent disease, to post-mortem change or to some toxic action, is for the neurohistologists to decide. Much of his research was incorporated in his two textbooks, first in 1882, *The Human Brain: Histological and Coarse Methods of Research*, and secondly his well-known *Textbook of Mental Diseases*, first published in 1889, a second edition of which appeared in 1898. Bevan Lewis retired in 1910 and was succeeded by Joseph Shaw Bolton, who while at Claybury, had done some important work on the structure of the cerebral cortex in mental diseases. He also invented an important modification of the Weigert-Pal stain for myelinated fibres which could be applied to frozen sections. He continued in the tradition of Wakefield and in 1914 published his well-known book entitled *The Brain in Health and Disease*. He retired in 1934. It is sometimes forgotten that during his period of office he initiated, in conjunction with Leeds University, the first D.P.M. examination in this country.

Meanwhile, in 1893 Sir Thomas Clouston, who for some time had been Superintendent of the Royal Edinburgh Asylum, secured the services of Dr. William Ford Robertson, who had for some years worked at the Edinburgh Royal Infirmary in pathology. In 1894 Ford Robertson commenced active work in collaboration with Dr. James Middlemass on the pathology of the nervous system in relation to mental disease. He was chiefly concerned with the neuropathology and histology of the nerve cells and nerve fibres. Ford Robertson's research gained him an immediate reputation. Clouston was quick to realize the importance of this work, and with his colleagues initiated what was known as the Scottish Asylums Pathological Scheme, with a joint laboratory and pathologist, for the promotion of study and research into the pathology of the insane. William Ford Robertson was appointed as the first pathologist under this scheme in 1897. Grants for assistance soon came in from the Medical Research Council, the Carnegie Trust and other bodies. He retained this post for a quarter of a century and, as is well known, later diverted his attention to bacteriology, especially to the actions of the toxins of diphtheroid bacilli.

In 1893 a sub-committee was set up by the L.C.C. to advise on research in pathology in the L.C.C. asylums, and also to encourage research by young medical officers. This report was eventually approved by the Asylums Committee and the expenditure of £4,000 was authorized for the building of a pathological laboratory and museum at Claybury Asylum. When the laboratory was opened, Dr. Frederick (later Sir Frederick) Mott was appointed the first Pathologist to all L.C.C. asylums and Director of the Laboratory. All his early work was done at Claybury, for although Henry Maudsley made his generous donation in 1908, which eventually resulted in the foundation of the Maudsley Hospital, Mott was not able to transfer his laboratory

there until many years had elapsed, albeit before the Maudsley Hospital opened officially in 1923.

By 1910 scientific tools available for somatic research in mental disease had undergone a considerable change; moreover Freud, Jung and Adler were already looming on the horizon. In the years before the first world war neuropathology had seemed to have spent itself and bacteriology was on the wane, but biochemistry and physiology were beginning to assert themselves. It was at about this time that another epoch in the investigation of psychotic illness in mental hospitals began. A new mental hospital at Whitchurch, near Cardiff, was opened under the superintendency of the late Edwin Goodall who had received most of his earlier training at Wakefield. Goodall was alive to the possibilities of the new science of biochemistry and persuaded his committee to build some first-rate laboratories and to appoint Dr. R. V. Stanford as a full-time research biochemist. While maintaining their interest in general pathology and bacteriology Stanford and Goodall concentrated their efforts on the abnormalities in the body fluids of psychotic patients. Stanford and his colleagues carried out much useful work and had support from the Medical Research Council. Thus, in 1912 he demolished the hypothesis that indicanuria, so often found in the insane, was due to intestinal putrefaction, and showed that these indole compounds were really a product of abnormal tryptophane metabolism. I mention this because today biochemists are much pre-occupied with the metabolism of these compounds with an indole ring. However, little notice was taken of his paper at the time. There can be no doubt, however, on the whole that the laboratory came a little before its time. Ignorance in our basic knowledge of biochemistry (e.g. enzymology, carbo-hydrate metabolism, energy-producing mechanisms, etc.) was too much of a handicap for any real advances to be made. By the time his successor, J. H. Quastel, a pupil of Gowland Hopkins, took over in 1928 the position had improved and tremendous progress in this field was to ensue in the coming 30 years. This research department first initiated by Goodall has now grown into the well-known M.R.C. Neuropsychiatric Research Institute.

It might seem irrelevant to the subject under discussion that the development of these mental hospital departments should be stressed, but it is done firstly to demonstrate that up to the end of the first world war and a few years after, the medical schools and universities had done practically nothing to promote teaching, study or research in psychiatry, and secondly to show that a few mental hospitals properly equipped and staffed can adequately serve not only as a training ground but also as centres for research in psychotic as opposed to neurotic illness. From 1920 onwards until the 1930's but few new developments took place in the mental hospitals. Whereas in the psychiatric out-patient departments of the teaching hospitals and general hospitals interest grew in the new movements of dynamic psychology and sociology, in this aided by Freud, Jung and Adler, the mental hospitals were still very much isolated and, with one or two honourable exceptions, had no out-patient departments up to and until January, 1931, and they dealt solely with certified psychotic patients. Their influence in the scientific world was definitely on the wane, especially owing to the development of large post-graduate hospital and teaching hospital departments. That the centre of gravity had moved to the teaching hospitals cannot be doubted. I would like to quote from Professor Mapother's address to this Society in 1934 regarding scientific research: "The first point to emphasize is that opinion concerning psychiatry in England is far too largely formed by those in practice. Therefore not only is it unduly

optimistic, but of a kind which dispenses with the laborious observation and experiment that forms the basis of every progressive science. It must be recognized that under modern conditions really important research cannot be a hobby for the leisure of those in either institutional or private practice. The army of science cannot be a militia—techniques are too difficult. Likewise it cannot be entirely a short service army."

The development since that time to the present is familiar to all. Scientific work in mental hospitals was definitely not fashionable any longer. The advent of new physical treatments gave much more immediate returns. All scientific work seemed to be centralized in one gigantic post-graduate hospital. Chairs of psychiatry were founded in many provincial universities, a number of medical schools acquired psychiatric beds and rosy views about psychiatric research in universities were put forward up and down the country. A new era seemed to be dawning in the field of research into mental ill-health.

In most aspects of our discipline this optimism has undoubtedly been justified. The advances made, for example, in physical treatments, rehabilitation, psychosomatic medicine, epilepsy, child psychiatry, group therapy and the like, are well known to everyone. When we consider the problem of the functional or endogenous psychoses, however, the picture is entirely different. It is unreasonable, and one might say in present circumstances inconceivable, to expect the medical schools or university departments with their strictly limited number of beds to undertake long-term serial scientific research on psychotic patients, which involves daily biochemical, neurophysiological and clinical investigations, spread over many weeks or months, or even a year. Experience has shown that isolated observations on a large number of psychotic patients have only been of value in a limited number of instances, or even perhaps of greater value in providing exercises for our statisticians, but in so far as they give us a clue to the metabolic changes in these patients they have been of no value at all.

The credit for starting the long-term intensive investigation must go to Dr. Rolf Gjessing, whose death last March was a great loss to psychiatry. In this connection I would like to quote what the late K. F. Scheid, who worked at the Kaiser Wilhelm Institute in Munich, said in an article in 1937. Scheid was the author of a well-known monograph on "Febrile Episodes in Schizophrenia". Speaking of what he called the concept of the polyphasic reactions of a pathological process and the need for serial investigations, he says: "The recognition of this technique in the investigation of the somatopathology of the schizophrenic psychoses has only very lately begun to bear fruit. Only Gjessing has taken seriously the demand for serial investigations, and in this way he was able to demonstrate interesting results. On the other hand, by far the greatest number of German investigators have confined themselves to a statistical evaluation of diagnosis in which a certain chemical or physical method has been applied to show how these results were characteristic of schizophrenia itself. However, as we are, throughout, dealing with polyphasic reactions one is bound to reach contradictory results, quite apart from the fact that, during a period of time, the changing morbid processes could not be recorded." This is the independent view of someone who had for years adopted this particular technique. I may be forgiven, perhaps, for quoting what Gjessing himself wrote in 1950. Speaking of the schizophrenias he says: "It is clearly not enough to investigate a small part of the whole complex of functions for a few days or weeks only. We cannot assume that functional (i.e. metabolic) disturbances are the same at the beginning, at the climax or in the terminal stages of an illness, for instance in hypertension, diabetes or tuberculosis. So

long as we do not know which disturbances are of importance we have to record a series of representative functions from several ranges at the same time. These functions may be more or less related to each other but probably not always to the same extent. The correlated psychic condition must be recorded day by day along with the rest, even if the psychosis itself is a terminal symptom occurring when the fundamental metabolic disturbance has reached the limit of psychic adaptation." His classical work on periodic catatonia is well known to everyone.

In view of the state of confusion with regard to the diagnosis of schizophrenia Gjessing warned us that unless we are sure of the homogeneity of a group of patients it is better to start with a single one. He maintained that such a complete and well-planned investigation of the endogenous psychoses is the only one which is likely to yield any results. In the same paper he goes on to say about the problem of schizophrenia: "Team work by specially trained workers in physiology, biochemistry, enzymology and clinical research is essential, together with enough assistants of every sort—research workers keen on the task and willing to work like desperadoes even for years on this particular problem. It is an undertaking for which the State will have to defray the expenses. However, if we regard the problem even from the viewpoint of the national economy, we can assert that as the State is spending millions annually on the unproductive permanent maintenance of mentally disabled patients, it would not be unreasonable to devote, say, one per cent. of this expenditure to finding out if it is possible to reduce the main cause. Every accurate observation, seemingly unimportant, may be of value because it may lead to further knowledge. Investigation of this kind may give no rapid returns but the reliability of the results will compensate for that. Many short cuts have been tried during the past half century without success, and now an investigation on a really adequate scale is justified." This is the main thesis on which scientific research in a number of strategically placed mental hospitals should be based.

There are few who today would argue against the view that the functional psychoses are caused or precipitated by humoral changes in the organism, however or wherever these may originate. Indeed this was the view of Henry Maudsley as expressed in his book (1867). The opinion that they are entirely of psychogenic origin must now be regarded as unreasonable in the light of our present knowledge.

The last decade has seen a great surge forward and a renewed interest in neurophysiology, neurochemistry, neuropathology and above all in neuropharmacology. With the exception of neuropharmacology the advance in these disciplines has been chiefly on the experimental and fundamental side. The Institutes in the United States, notably those at Bethesda, St. Elizabeth and Illinois, together with some of the newly-founded professorial chairs at the Maudsley Hospital, exemplify this development. Mental hospitals, on the other hand, are doing less scientific research today than 30 or 40 years ago. It cannot be true that this is due entirely to a lack of enthusiasm: rather has there been a shift of emphasis because the scientific approach seems to have been much less rewarding in giving immediate results. Many progressive mental hospitals today are preoccupied with therapeutic trials and experiments in community care, group therapy and rehabilitation, and the phenomenology and ecology of mental disorder, whereas previously laboratory work was emphasized. Clinical psychologists and social therapists are now multiplying everywhere. It would be foolish to deny that these developments have been of immense and lasting benefit to our psychotic population in hospitals, but is it right

that scientific work in the disciplines mentioned above should be almost entirely discouraged? The view is taken in some quarters that serious scientific research must not be undertaken at the periphery, but must all be concentrated in the university centre. The argument is that keen young men with ideas and a flair for original work must be in constant touch with experts and receive the benefit of constant interchange of ideas and healthy criticism, whereas this is not possible for the research worker ploughing a lonely furrow in some distant mental hospital. This may be true in theory but in practice it is far from being the case. Further, research into psychotic illness has been entirely equated with research in other disciplines such as internal medicine, pathology, ophthalmology, etc. As long as this view predominates little or no progress can be made in the multi-disciplined long-term investigation of the endogenous psychoses after the Gjessing pattern. Progress has been made even more difficult by the administrative set-up since the National Health Act was introduced. Whereas the medical schools and universities have not suffered, the few mental hospitals engaged in this type of work have to endure a general lack of interest and understanding on the part of some Regional Hospital Boards. Except for the most elementary form of clinical research, schemes cannot be entertained or staff be appointed by the hospital authority unless the project has been vetted by one or more advisory committees, one of which is almost certainly to be a research advisory committee composed largely of non-psychiatric medical men, the majority of whom lean towards the university centre, and have, understandingly enough, a complete lack of appreciation of the problem. Even research grants from well-known voluntary bodies, who have put up money for a project sanctioned by their own professional advisers, may be the subject of this veto. It would be unfair to blame the Regional Hospital Boards for this state of affairs. Their primary duty is to administer the hospitals of their region efficiently. They are not usually bothered with this perplexing research item from other disciplines. Their responsibilities in providing the necessary facilities and allowing the use of certain hospital services are freely admitted, but whether it is reasonable to place upon them the onus of deciding whether a research project should be supported is indeed open to question. Furthermore, one gains the impression that Regional Boards and their officers would rather be without this invidious task. Where a mental hospital with scientific interests is not linked administratively to a university department a new approach, therefore, to this problem seems ripe for reconsideration. A more positive line by the Clinical Research Board could well be pursued without necessarily infringing on the democratic principles at the periphery.

It might well be asked what are these lines of research that should be undertaken in well-equipped and strategically placed mental hospitals. It is clearly beyond the capacity of one individual to give this answer. All one can say is that within recent years promising results have been obtained with new techniques and methods which are particularly well adapted for the serial and prolonged study of psychotic patients. This implies that a research worker appointed, in biochemistry for example, must have facilities for adequate technical assistance, not only for applied work in the clinical field, but also for pursuing basic and experimental research, and enjoy the same freedom which is enjoyed by his colleagues at university centres. There should be other special departments in a hospital of this kind, particularly electroencephalography, psychology and even neuropathology, to assist in the recording of data in a long-term serially devised undertaking. Lastly of course a fully trained clinician

must serve with this team. Mapother in 1934 suggested that each of those selected for knowledge of a particular science should have a training of a year or two in psychiatry so that he shall have a live feeling about its real problems.

There is no lack of projects, but it would be found of great advantage to investigate day by day and week by week over several months psychotic patients who show a periodic variation in their mental states, and to attempt to correlate any changes in the scientifically recorded observations with alteration in clinical status.

To refresh your memory I would like to refer to Gjessing's results in periodic catatonia. Details of his thorough and systematic approach can be read in the original. His experimental set-up, which it was my privilege to see at one time, was such that it attempted to eliminate all sources of error. A large number of observations were made daily, e.g. pulse rate, blood pressure, body temperature and bodily movements, basal metabolic rate, blood sugar, alkali reserve, and the excretion of nitrogen, sulphur and phosphorus. The main finding was that in this form of catatonia there was a marked nitrogen retention, a large amount of nitrogen being stored in the body. After a certain period, when the retention reached its peak, the store was completely emptied, being excreted in the urine in various forms. This coincided with a change of phase in the illness, usually the onset of stupor. His work has largely been confirmed by others, but apart from his findings the main interest lies in the new methodology he evolved.

This method has been applied in other fields, e.g. in the study of water metabolism in epileptics carried out by Greville and Tudor Jones, where three epileptic patients were examined daily for water retention and water excretion, two over a period of 5 months, and one for 3 months, control observations having been made on one non-epileptic patient. The object of the experiment was to determine whether there was any connection between the incidence of grand mal seizures and the exchange of water between the epileptic organism and its environment. The original paper can be consulted. The main findings were that changes in the fasting body weight under controlled conditions afforded a fair measure of the changes in body water. At most, 10 seizures out of 22 were preceded by a rise in the weight curve, and 10 out of 22 by a fall. This painstaking and time-consuming work rebutted the findings of Stubbe-Teglbjerg and demonstrated that the retention of water does not by any means precede a seizure. A negative water balance was observed after more than half of the isolated seizures. Unfortunately at this time electro-encephalography was in its infancy; continuous tracings could not therefore be done. In this instance then, the periodicity was supplied by the occurrence and recurrence of fits.

More rewarding subjects of study are manic-depressives, especially those cases showing recurrent attacks, circular and alternating insanity. H. Tomasson, as early as 1924, demonstrated disturbances of ionic equilibrium in blood electrolytes in manic-depressive psychosis, and claimed that the deviation from normal occurred before the onset of the pathological phase. This involved months of daily estimations and accurate clinical observation. He was specially interested in the calcium-sodium ratio of the serum, and he claimed to have shown that, as he put it, "the heightened emotional tone was accompanied by increased serum calcium and diminished serum sodium". He claimed to have demonstrated that there is a marked alteration in the calcium-sodium ratio which profoundly affects the metabolic and especially the vegetative functions. These changes may of course be secondary to other metabolic disturbances,

but at any rate they are facts which are of interest and can fit into any general metabolic projects on manic-depressive psychosis.

In 1954 John Dawson and his colleagues in Leeds, starting from the hypothesis that there might be a disturbance in carbohydrate metabolism in manic-depressive illness, investigated the blood acetoin (i.e. acetyl-methyl-carbinol) in both the manic and the depressive phases of the illness. Their investigations up to now have shown that there is an increase of the acetoin level in depressions and a decrease in the manias, as compared with the normal. Further studies under controlled conditions are now being conducted by Dawson at Runwell, in association with his colleagues on the clinical side and in the EEG and psychology departments. It is hoped that by such longitudinal studies further and more accurate data will be available showing the variations not only in the type of illness, and whether the changes precede the illness or not, but also the effect of treatments. At the same time, experimental and fundamental work is going on in the laboratory on the acetoin metabolism and the effect of potassium depletion. A great help in this work has been the provision of a small metabolic ward of two beds with the necessary nursing staff. Such a ward being only about 30 yards down the corridor from the main laboratory is an enormous advantage to the research worker.

During 1956 and 1957 Weil-Malherbe and the writer were able to show differences in the urinary excretion of catechol amines, that is adrenaline and noradrenaline, in the manic and depressive, and normal phases, in 3 patients with periodic attacks of manic-depressive psychosis. In two of these the manic and depressive phases alternated rhythmically. They were studied serially, and in one case for more than a period of six months. In addition, a number of grouped cases were investigated in which a number of samples were obtained during the pathological phase and after recovery. A significant increase of sodium and potassium excretion during the manic phase was also observed in one patient. Crammer, working in Birmingham, studied sodium and water metabolism in 2 chronic psychotic patients with recurring mental disturbances. Weight loss was accompanied by polyuria with increased secretion of sodium chloride, weight gain by the opposite. In one patient Crammer demonstrated loss of sodium at the beginning of an attack of depression, in the other just before the emergence from a depressive state and the start of a hypomania. He suggests a disturbance occurring centrally, probably in the hypothalamic endocrine system. It is also of interest to note that, in view of the great attention paid to serotonin metabolism recently, we found the excretion of its breakdown product, 5-hydroxyindoleacetic acid, increased in the manic phase in the two patients examined for this. Our determinations of this substance, however, were of a preliminary nature and the results need to be confirmed. The *main* constant result obtained in this investigation was a higher excretion of adrenaline and noradrenaline during the manic phase than during the depressed phase. There was also a tendency, although we have made no claims, for the excretion of adrenaline in the depressed phase to be lower than in the normal phase.

Bergsman, working in von Euler's department at the Karolinska Institute in Stockholm and largely with mental hospital material, has within the last two months published a monograph entitled "The Urinary Excretion of Adrenaline and Noradrenaline in some Mental Diseases". These patients were not examined serially, but samples were taken at least twice in the majority of cases during the pathological phase and four times in one case of mania. The results confirm the increased output of these two amines in the manic

phase, and the diminished output in the depressive phase as compared with normal controls. They also investigated schizophrenics, acute and chronic, senile dementias, phenylpyruvic amentias and neurasthenias, and the reaction of all groups to injection of insulin. As far as manic-depressives are concerned these two conditions are regarded as at opposite poles for respective excretion of adrenaline. He tends to the view that there is an endogenous factor which is responsible for the high and low production of adrenaline respectively. The results obtained by Bergsman agree closely with those obtained by us.

No doubt many more examples of this type of work could be given: for instance, the serial work in endocrinology such as was carried out by Hemphill and Reiss, repeated electroencephalographic recordings in conjunction with clinical and biochemical investigations before, during and after specific treatments. The state of drugs now on the market affords ample opportunity for this type of study, and indeed such investigations are already under way. Surely it is only by such means that we can continue to collect facts which may eventually lead to a more rational form of treatment.

As one last word about the scientific approach to psychotic illness I would like to make a strong plea for the more extensive use of the science which has been grossly neglected in this country for the past 40 years, namely neuropathology. Professor Sir William Le Gros Clark stated in Oxford in 1952 that "the fundamental requirement is the study of human brain material, particularly when we know quite a lot about the patient during life". He stressed that a more intimate knowledge of the anatomical organizations and actions of certain regions of the human brain which remain very obscure may contribute quite important information regarding the physical correlates of mental disorders. Professor Meyer also described long-term studies of individual variability in the cortical cyto-architecture of normal brains. He suggested that this variability may not be haphazard, and that if we had the patience and facilities for such time-consuming investigations we might well arrive at interesting correlations between abnormal personality and brain morphology. With modern developments in staining technique, in cytochemistry and the advent of the electron microscope, there is undoubtedly a vast field of work waiting to be done. The advent, too, of neurosurgery in mental illness provided a stimulus for neuro-anatomists and neurophysiologists. Degeneration in the dorso-medial nucleus of the thalamus has been demonstrated by the results not only of standard leucotomy but also following the more circumscribed operation of orbital cortex undercutting, at least in two cases. This links with experimental work on the connections of the thalamus, hypothalamus and the frontal cortex. The central connections of the temporal lobe are virtually unknown, and suitable material must eventually come to hand from patients who have undergone temporal lobectomies. The few neuropathologists working on these problems cannot possibly cope with the many projects waiting to be done, both in psychosis and mental deficiency. The advantages of a close link-up between a university department and a hospital in the field must be obvious to everyone.

Some of these projects may be rewarding in the near future; most of them, however, are only part of a process of building up facts and data for further elaboration which may take decades, if not generations. Each advance made now will give fresh clues for others to work on, and the modest but definite information that has been obtained in these fields convinces me that further effort is certainly worth while. One of the greatest dangers is expecting too much too soon, as this may divert both men and money into other fields.

In the foregoing an attempt has been made, however inadequately, to put

before you examples of the kind of project that seem to me to be eminently suitable to be undertaken in a mental hospital research department, and to be complementary to that being carried out in our universities and post-graduate schools. The question of recruitment of young men and women of the right type to this work inevitably prompts a brief word on undergraduate and post-graduate education. If one has had an opportunity of learning from the reactions of men and women who pass through the various grades of appointment in a hospital one gets quite a good general impression of their attitude towards both undergraduate and postgraduate education, and a great deal can also be learned from the current opinions held by our consultant colleagues in general hospitals.

Firstly, as regards undergraduate education, I have no doubt that Professor Sir David Henderson summed up the situation extremely well when he said in 1952, and I quote: "I think the first thing to do is to get the co-operation of our medical colleagues. Ours is still a branch of work that is not regarded in university circles as being of anywhere near the same standing and importance as general medicine, surgery and the rest of it. I think we should educate our own profession in regard to the place that psychiatry has to take. I believe that every medical student coming into the medical school for the first time should know that there is something in addition to a body, that there is a mind, and that later he may be required to treat the disorders of the mind that are likely to occur in his practice, whether he is in general practice or any other branch of medicine." A little later he says: "There should be an examination in psychiatry as part of the final clinical examination." No one in this hall I believe would argue against Sir David Henderson's thesis, when one remembers that more than one-third of the cases seen by a general practitioner are neurotic or psychosomatic in nature, and that over 40 per cent. of the hospital beds in this country are occupied by psychiatric patients.

The standard of our undergraduate education has now reached a high peak of excellence. Chairs have been founded in provincial universities and much has been done under difficult conditions, but the psychological effect on the student of having to learn a subject in which he is not required to take an examination is, I venture to say, damaging to the status of our specialty. It must be unique in any academic circles in the world for a professor to instruct undergraduate students in a subject in which they are not required to take an examination. In this way the position of our subject in the curriculum continues to suffer, particularly among our consultant colleagues in other branches of medicine. Furthermore, what is lost during undergraduate days can never quite be regained by postgraduate instruction.

Postgraduate facilities available in this country are some of the best in the world, but more emphasis could be laid on informal rather than formal education whose aim is a specific examination. One can only point out what seem to be anomalies. Whilst special examination is vital and the higher qualification very desirable it may be argued that an abnormal emphasis is placed on a higher qualification in general medicine. One finds that many young people take a large amount of study leave and spend unnecessarily a great deal of time in attempting to obtain such a qualification. If the undergraduate teaching in general medicine is sound and the postgraduate experience in a general hospital is adequate this should in all conscience be enough for anyone who wishes to specialize in psychiatry. If this rather outmoded insistence on a vast knowledge of general medicine is necessary it can only have a frustrating effect on many of our younger aspirants to psychiatry. There are

other disciplines which they could study with greater advantage, or, alternatively, better use could be made of study leave to visit clinics abroad, rather than to be preoccupied with the complications of smallpox or the mysteries of collagen diseases. Again, conditions must be made attractive and it does not help to denigrate the mental hospital and to encourage the view that mental illness of whatever kind can equally well be treated in a general hospital, which more often than not lacks the special facilities required for all types of cases. A sense of proportion is required if we are not to do a disservice to the public. The fact that a mental hospital has to keep its failures has a salutary effect on therapeutic enthusiasts *vis-à-vis* their colleagues in a psychiatric unit of a general hospital, whose failures can be transferred to the appropriate mental hospital and be forgotten.

However things may turn out after the new legislation is introduced there can be no doubt but that the mental hospitals will continue to treat the bulk of the functional psychoses who require a fairly prolonged stay. This has been confirmed in countries where psychiatric in-patient units in universities and general hospitals have existed for many decades. Indeed, an equilibrium has been reached abroad as it no doubt will do here. In Scandinavia, for instance, at least three of the professors of psychiatry are heads of mental hospitals, a fact which serves to demonstrate the importance attached to the long-term study of psychotic illness.

One may be forgiven for not emphasizing sufficiently the many other developments in psychiatry, but this has been done so ably by others. These remarks serve only as a plea that, with all the progress made in social forms of treatment, group therapy, community care and rehabilitation, and last but not least, in empirical treatments, we must not forget that as long as there is a small chance of success some of us have a duty to tread the unpopular and wearisome path of constantly applying newly-discovered scientific methods and techniques in the longitudinal study of psychotic illness, in the hope that our successors may one day, perhaps generations hence, find further clues to some at least, if not all, of these disabling conditions.

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SOME RELATIONSHIPS BETWEEN THE PSYCHIATRY OF CHILDREN AND OF ADULTS*

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FOR the Chairman's Address to the Child Psychiatry Section in 1955, Cameron (5) decided to survey the scene of Child Psychiatry. His survey was historical and he described the various influences that have in turn borne on and helped to shape the practice of Child Psychiatry as it is today. Kanner (9), in the Maudsley Lecture of 1958, took the same theme and elaborated on it further. It is significant that they both felt that the time had come to do this for a young speciality and, indeed, their lectures were of considerable interest and use to those of us who have not lived through—in Child Psychiatry—the times described. However, Child Psychiatry has not become static; the scene will continue to change and to enlarge as more new influences come to bear. It seems that we who are engaged in its active practice now, and in the future, have need to watch where we are going; especially, as comparative success has brought some rewards and we foresee the likelihood of further rapid expansion in the speciality, with the need to recruit more child psychiatrists. Again, the joint or liaison committees that have sprung up with other medical professional bodies are in a sense a recognition of our significance; they are also a responsibility and may be a test of our loyalty to psychiatry as a whole.

Cameron and Kanner both touched on the relationship of the psychiatry of adults to that of children and described how, early on, psychiatrists working in the adult field tried to apply their knowledge of adult patients to children. Kanner, almost apologetically, took Ziehen (18) as an example who, in writing his treatise on the mental diseases of childhood, as late as 1925, must, Kanner (9) felt, have proceeded in the following manner: "My readers are, of course, familiar with paranoia, melancholia, hebephrenia, stupor, hysteria, etc., in adults; now let us see how frequently these things are seen in children and how similarly or dissimilarly they manifest themselves." Both lecturers quickly went on to spend much more time on the important funds of knowledge that other disciplines, mostly outside psychiatry, have contributed to the practice of Child Psychiatry as it is today. It has become a dynamic subject, dealing as it does with the growing child; and, enriched by the psychodynamic approach and much else already outlined by Cameron and Kanner, it could only leave behind such seemingly sterile concepts as those of Ziehen.

On the other hand, both the psychopathologically orientated schools of thought and the psycho-biological approach of the Meyerian school have emphasized from their different viewpoints the continuity of Child Psychiatry

* Chairman's Address to Child Psychiatry Section, Royal Medico-Psychological Association, 12 November, 1959.

with Adult Psychiatry. After all, "The child is father to the man" (Wordsworth). Psychiatry needs to be viewed as a whole; if some practise Child Psychiatry by choice, others may have to exclude practice with adult patients because of pressure of work. The total field of psychiatry has become too large and it has had to be divided. However, how far some child psychiatrists have shied away from the concepts used in the practice of clinical psychiatry with adults is illustrated by Winnicott (17) who has stated: "The harm done to Child Psychiatry would be consolidated should Child Psychiatry become part of Adult Psychiatry, a fate which it has so far avoided." It is not in fact likely that Child Psychiatry can become part of Adult Psychiatry in the way that Winnicott fears, but this Children's Section is significantly a Section of the Royal Medico-Psychological Association, a position that has enriched the former in many ways. Winnicott went on to say: "Child Psychiatry has more to offer to Adult Psychiatry than the latter has to the former." This may up to a point be true if psychopathology is under consideration. It may become true as far as descriptive psychiatry is concerned at some future date, but up to the present it is likely that colleagues working in the field of Adult Psychiatry have not gained from Child Psychiatry as much as they may have hoped to do.

Child psychiatrists are pre-occupied with the assessment and treatment of the immediate and pressing problems that children present. They may also pay attention to what can be done to prevent their development in the first place. They are on reasonably firm ground in their predictions for the near future of their patients. There can as yet only be speculation as to what sort of adults they will become. Few such patients have been followed up into adulthood and certainly not in sufficient numbers to allow any worthwhile conclusions to be drawn. The practice of Child Psychiatry has been too recently established and the war years have intervened. There are, of course, important studies under way; for instance, that of the University of London, Institute of Education and Child Health, Child Study Centre (Moore *et al.*, 12). Detailed as this is, it involves comparatively small numbers of potentially healthy children; it is not primarily concerned with disease processes.

On the whole, it seems that patients as they mature may often be viewed in cross section rather than in longitudinal section. Child psychiatrists naturally have ample clinical experience of children of all ages. Then, somehow, there are adult patients with their clinical characteristics, sometimes viewed by the child psychiatrist in a sense at secondhand, as parents. There is an ill-defined gap between the two, with adolescent patients placed uneasily somewhere in it, rather unhappily dealt with either by the adult psychiatrist or by the child psychiatrist. An adult patient naturally has a past history of childhood, but there is seldom opportunity to view this through the eyes of a child psychiatrist and memory is usually too short for accurate recall. In other words, knowledge of the phenomena showing in psychiatric ill health, as it stretches through childhood into adulthood, is on the whole rudimentary. It is more meagre, perhaps in the neuroses and character disorders than in the psychoses. Child psychiatrists, however, need such knowledge for long-term prognosis. Adult psychiatrists may be helped by child psychiatrists having traced forward more accurately, not in this connection in the psychopathological sense, the phenomena to be found in psychiatric ill health through earlier age levels; the natural history of mental ill health. This is a way of looking at Child Psychiatry and its relationship to Adult Psychiatry, which is the opposite to that of Ziehen.

The lack of opportunity to carry out long-term studies in Child Psychiatry into adulthood has left a hiatus, which has not been filled by psychopathological

theories of aetiology. Mayer-Gross and Slater (11), in the chapter on "Child Psychiatry" in their textbook, it seems had this in mind, when they expressed criticism of facile optimism sometimes expressed by child psychiatrists, when judging the long-term value of their work: "The hope of preventing by psychiatric supervision or treatment in early life a large part of adult maladjustment or illness is even less substantiated (—than that the origin of neurotic and psychotic illness of adult life is to be found in the experiences of early childhood). All that the present state of our knowledge justifies is the hope that in some cases, which we may eventually learn to identify, the chances of illness or abnormality would be materially reduced by sane and healthy upbringing." They emphasize that the psychoses are found to be quite uninfluenced by early upbringing, home life and childhood experience. Are child psychiatrists in a position to refute this? Again, they point out that the more serious psychoses of adulthood, or severe neuroses based on constitutional psychopathic abnormalities, are rarely seen in children, or develop at that time of life to a stage where recognition is easy. May not long-term studies of child patients with psychiatric disturbance, followed up into adulthood, shed further light on these?

Many of the psychiatric disturbances of childhood, perhaps largely reactive to the environment, tend to settle down with suitable handling or sometimes without special treatment, and so allow healthy development to proceed. Other disorders, however, having started at some age or other in the first or second decade, seem to continue, sometimes unperceived or perhaps with intermissions; and, in spite of all efforts to treat them in childhood, develop into the well-known psychiatric disorders of adulthood. How far can these cases be picked out and how can they be better understood? Curran (7) in his presidential address to the Section of Psychiatry of the Royal Society of Medicine in 1951, pointed out that clinical studies are essential for the solution of the clinical problems of diagnosis, prognosis and treatment, and asked who could doubt our ignorance of the natural history of many disease groups. Have we, in fact, got much beyond Hector Cameron (3), who in 1919 wrote: "In children beyond earliest infancy we recognize a gradual approach to the conditions of adult life. Fractiousness and naughtiness, ungovernable fits of temper, uncontrollable weeping and inexplicable fears should disappear with early childhood even if management has not been perfect. If they persist to older childhood we shall find in an increasing percentage of cases evidence of definite neuropathic tendencies, which urgently call for investigation and for a precise appreciation of the nature of the abnormality."

It is now proposed to indulge in speculation, using clinical material as anecdotes to try and illustrate some of the links between the psychiatry of childhood and that of adulthood. Such are well known, but how far have they been studied prospectively as opposed to retrospectively?

It happens that follow-up material is now available from the in-patient unit for adolescents established in 1949 at Bethlem Royal Hospital and which has been described elsewhere (Cameron, 4; Warren, 16). This material consists of 187 patients, of whom 157 were followed up, discharged, aged 12 to 17 years old, between 1949 and 1953, and who have now mostly reached the early twenties. These patients were under the care of Dr. Kenneth Cameron or myself; and it is hoped that this follow-up material, which is being statistically analysed by Dr. Lilli Stein and myself, will be produced elsewhere. It has been collected from up-to-date reports and, in a majority, from follow-up interviews of relatives by psychiatric social worker colleagues, and of some of the ex-patients

by myself. The data so obtained from the case notes and follow-up information require careful and uniform classification and statistical evaluation; and although such classification loses some of the individual "life" of each patient, this is the only way to evaluate the group-characteristics of each diagnostic category and to examine their common features and relationships. In the present paper, however, some of this material is being used to provide illustrations in terms of individual cases.

An advantage of adolescent patients is that a fairly recent account of their earlier childhood can be obtained, although even then recall of infant years by parents is not always accurate and occasionally not available at all. Their follow up six to ten years later meant that they had, or nearly had, reached adulthood. Even so, only the first few chapters of their lives have been written and much can happen later on. Nevertheless, the "plots" of their life stories have sometimes now been revealed.

Such material is most heterogeneous, including the psychoses, not to be considered here, a wide range of neurotic disorders, behaviour and conduct disorders and disturbances of personality. Some patients' illnesses were typical of the familiar childhood syndromes to be met in the practice of Child Psychiatry, others were more adult in form. A small proportion only can be used here, but it should be emphasized that when the material is examined as a whole, its outstanding characteristic is the overlap that occurs between the symptom-complexes and syndromes shown by these patients, including often the psychoses; they shade imperceptibly one into another, as do their personality structures. Certain groups can be picked out with outstanding features common to them, but there is usually no clear-cut division separating such groups from other patients. This is typical of the adolescent period of life, when all is, in any case, in a state of flux.

It is proposed here to make use of three groups of patients, whose subsequent careers often happen to appear rather discouraging to the earlier efforts of the child psychiatrist. To reassure ourselves, however, many others with various kinds of disturbance and who achieved stability, could have been picked out; they would not have been suitable to use for the present proposition.

PHOBIC STATES, INCLUDING SCHOOL PHOBIA

At the N.A.M.H. Child Guidance Inter-Clinic Conference of 1959, the subject of "School Phobia" was discussed. Inevitably, much time was spent on the nature and aetiology of the underlying condition and how to treat here and now these children, who have such a troublesome presenting symptom. The accent was on the present rather than on the future. However, Burns (2), when summing up the conference, quoted Johnsen (8), who stated in 1941 that school phobia was "in line with other phobias and we need not think it stops with childhood, it can go on to the age of 50". Burns asked if school phobia was allied to the crippling disease of agoraphobia and also quoted a case he had followed up, who had later sought help for neurotic symptoms when a young adult, after an interim period of stability. He postulated sometimes a constitutional element in these cases, which he thought rather important and sometimes rather neglected.

As far as our experience is concerned, 16 patients, aged 12 to 16 years (7 boys and 9 girls), were admitted to the adolescent unit because of continued refusal to go to school, who had failed to respond mostly to treatment in child guidance clinics. There were 7 others where the school refusal was associated

with a severe neurosis, or in 1 case an early psychosis, which in fact made them unfit to go to school. The histories and clinical conditions of the 16 relatively uncomplicated cases did not appear to differ much from the many cases dealt with by other means, elsewhere; their admission was perhaps somewhat fortuitous. Their hospitalization did not necessarily mean they were more ill. They were all treated with varying success as regards their underlying condition and getting them back to school, but follow up shows that of these 16 patients, now aged between 18 and 22 years, 1 should be in hospital for a severe phobic state, 3 are severely handicapped by a phobic state, 3 live somewhat limited lives because of phobic symptoms and 3 more have shown since discharge other kinds of neurotic difficulties, but which appear to be settling. Six (under one-half) now appear to be quite well.

Five of these patients with refusal to go to school had at the time shown phobic symptoms apart from this presenting symptom. To these can be added three more phobics who, however, did not show school phobia. Of these 8 latter patients on follow-up, 1 has been leucotomized for continued phobic symptoms, 1 is in hospital and another should be with severe phobic states, 2 more are severely handicapped and 2 mildly handicapped by phobic symptoms. Only 1 patient can now be considered normal. It seems in this small group that the outlook was worse when school phobia was accompanied by other phobic symptoms.

Looked at in this way, there seems to be considerable overlap in adolescence between phobic states in general and school phobia in particular. Is this sufficiently recognized by child psychiatrists, with the prognostic implications for the former condition? Further, 3 of these patients also showed obsessional ruminations and it is believed that some of these cases shade off imperceptibly into the obsessive compulsive states. Others showed well-marked hysterical traits and so on. All these have implications for adult life, if they persist. During the time of admission, these adolescents' likely future psychiatric state as young adults was not always appreciated. In the first decade of their lives, they had mostly not had any particular symptoms, to forewarn of future adult ill health; in the second decade their illnesses were in fact unfolding in some of them. Here are some examples, in brief outline, which perhaps give further a different slant to the day-to-day clinical problems met in the second decade. To study larger groups of patients of this type in detail, might be enlightening in helping to trace out the early stages of such a crippling condition as the phobic states can be later on:

Emergence of a Severe Phobic State

1. *Douglas*. Admitted, aged 15 years, after 16 months previous treatment in another mental hospital. His father had early on been killed in action; his mother was an anxious, neurotic woman. Douglas was of average intelligence. He was always shy and sensitive and with tempers if frustrated. However, he was happy until sent to a Royal Navy boarding school at the age of 11 years. He became anxious, hypochondriacal and was further acutely upset by anaesthetics for appendicitis and a fracture. Acute panic attacks developed and he was sent home. He then became afraid to go out and was admitted to the first hospital, aged 14 years, and thence to us. It seems that he might have been a school phobic had he not been at boarding school. He made little progress in the adolescent unit, in spite of intensive psychotherapy and, after nearly 2 years, was transferred to his local mental hospital. He did not like it and went home. Here he remained unable to go out. He was sent to relatives for 2 years and then returned to his mother. He remained more or less confined to the house for 3 more years and had out-patient psychotherapy. He was then admitted to hospital again, aged 23, for more intensive therapy and to get him away from his mother. There he remains for the present. He has a severe phobic state. He cannot go out without acute anxiety.

School Refusal with Later the Emergence of a Severe Phobic State

2. *Raymond*. Admitted, aged 14 years, with a 9-months history of increasing refusal to go to school and tempers with his family. He had always been reserved, mixed poorly, quick tempered and had never shown affection. He had early on been frightened by air raids. His father was morose and lacked understanding; his mother ineffective; the marriage unhappy and home circumstances poor. He was of low average intelligence.

He remained in hospital for 11 months. He alternated between days of brooding or over-activity, but appeared to improve and become more outgoing. Psychotherapy was on the whole resisted.

After discharge, he seemed a good deal better. Within months he deteriorated and was charged as out of control and placed in an approved school. He failed to adjust and absconded. Aged 16, he returned home and became more solitary. At 17, he was admitted to a mental hospital for a few weeks and was given E.C.T. with some improvement. However, from this time until now aged 22, he has remained in his room, except for meals and to watch television. He has become passive, withdrawn, with vague fears and feelings of having committed a crime, if he meets people. The only job he attempted in a factory, he left as distressed by the crowds of people. He entertains himself with records, drawing and reading. He is having no treatment.

School Refusal, with Continued Minor Neurotic Illhealth and with Mild Phobias

3. *Pauline*. Admitted, aged 13 years, with a year's history of anxiety attacks, hypochondriasis and latterly refusal to go to school, following several months in hospital with rheumatic fever. She had previously been a happy and sensible girl, but always nervous, timid and over-dependent on her mother. Her father had paranoid schizophrenia and was separated from her mother, a very anxious woman. Pauline was of average intelligence.

She settled in hospital, soon became quite a tomboy and showed some bad behaviour. In psychotherapy she expressed hostility to her mother. She settled down and was discharged after 3 months. However, she relapsed and again refused to go to school and was readmitted for 6 months. She responded well and was discharged to go out to work.

She had a number of jobs, mostly in offices, and often stayed at home. She married at 19 years after 2 years courtship. She still lives with her mother and also her husband and baby, born when she was 20 years. She has had a number of minor ailments and fears to travel. With her husband, however, she had developed an enjoyable social life with a number of friends. She still suffers from attacks of nerves. She was sick through pregnancy and had a difficult delivery. After the birth, she again developed a vague illness called "rheumatic fever" and was in bed under the care of her own doctor. She is still very dependent on her mother.

School Refusal in a Boy of Dull Intelligence and with Continued Inadequacy

4. *Derek*. Admitted, aged 14 years, after several months refusal to go to school, after moving from the provinces to London and which led to a Court charge. He was sleeping badly and had temper outbursts. A shy, sensitive boy, always anxious and afraid of the dark. His father was away in the Army when he was young and subsequently took little interest in the family. His mother was inclined to depression and to be over-protective. An older sister had had a phobic illness for several years. Three other siblings were stable. Derek had had a number of physical illnesses, had been evacuated at the age of 2½ years, with a number of moves and probable neglect. He was of dull intelligence and had an inguinal hernia.

He settled down well in hospital, made friends and took an active part in everything. Much attention was paid to the mother, towards helping herself and her attitude to the boy.

Since discharge, the family has moved backwards and forwards to the provinces and is now settled in London. Father is in ill health and has not worked for 4 years. Family inter-relationships are poor. Derek has had countless jobs as a labourer. He has lost a number by failing to go. He has one or two friends and goes to dance halls to watch dancing. He has never had a girl friend. He still has his hernia and will not have it treated. He is immature and lacks initiative. He spends a lot of his spare time in bed. He is undoubtedly handicapped by his dull intelligence and lack of education. He is now aged 20 years.

In Contrast: School Refusal with a Subsequently Normal History

5. *Bevan*. Admitted, aged 12 years, for refusal to attend school for 9 months, following a minor illness. A child guidance clinic had been unable to solve the problem. Both parents were overanxious, but the home was otherwise satisfactory. He had always been over-protected; a happy, sensible, but strong-willed boy. He was of average intelligence.

He settled down well and appeared to be free from disturbance. After 3 months he was discharged to a boarding hostel for maladjusted boys, and while there he attended a secondary modern school. He seemed normal and made good progress. There was no further trouble; he completed 2 years National Service in the R.A.F. and has joined the G.P.O. as a technician; a job with prospects. He is now aged 20 years. His parents now ascribe his trouble over school to a certain teacher there.

THE OBSSIVE COMPULSIVE STATES

Obsessive Compulsive states, below the age of 10 years are uncommon, although children often and normally indulge in repetitive acts. In the same way, mild phobias are common early on; phobic states seem to be rare in the first decade. A young child is not yet a clinical entity in these respects; he is part of a family who are usually involved in such symptoms. A number of authors have touched on obsessional conditions in childhood; Pollitt (13), however, speaking on the natural history of Obsessive Compulsive states, analysed 150 cases retrospectively and showed that about 22 per cent. had had obsessional symptoms, as distinct from the present illness in adulthood, before the age of 10 years; 25 per cent. before the age of 15 years and 27 per cent. before the age of 20 years. As far as the present illness in adulthood was concerned, in 5 per cent. it had dated back to before the age of 10 years; in 12 per cent. to before 15 years; and in over 20 per cent. to before 20 years. The illness as a whole was phasic and tended to occur in bouts in childhood, adolescence and in adulthood.

In our experience, 15 patients were admitted between 1949 and 1953 with obsessive compulsive conditions, aged between 12 and 17 years, and followed up between the ages of 19 and 24 years. Five of these had also shown phobic symptoms at some time, and many in varying degree some of the mixed bag of symptoms indicative of disturbance early in childhood, familiar to child psychiatrists. In addition, there were 14 others who showed obsessional symptoms as part of some other psychotic or neurotic condition. However, of the 15 patients with a definite obsessive compulsive state, in 1 the illness began at 4 years, in 3 at 8 years and in 5 at between 9 and 10 years. In the rest, the illness was of fairly recent onset. On follow up, 1 has been leucotomized, 1 is in hospital with obsessional neurosis and 1 should be, but refuses treatment. Two more are severely handicapped by obsessional symptoms and 4 others somewhat handicapped. Four have a tendency to mild obsessional symptoms under stress. Two only are quite normal. Some of these patients can be said to have personality disorders with obsessional features; such could not, however, be readily separated from the rest of the group. Here are some examples, whose further histories will be of interest:

Continuing Marked Obsessive Compulsive State

6. *Donald*. Admitted, aged 15 years, with a long history of obsessional symptoms and phobias back to the age of 4 years. His father, a riddle maker, was critical and the patient had never got on with him; his mother, timid and with a history of Graves' Disease. One sister, 4 years younger, was normal; another died when he was 4. Always timid, obstinate and attached to his mother, he developed phobias and obsessional rituals at 4, after the birth of one sister and the previous death of the other. His legs were also in irons for 2 years at this time. He refused to go out for 6 months. He improved, but the rituals remained. They became worse at 9, and at 14, after slipping on some blood in the road, he became very much worse. He was of average intelligence.

During a year in hospital, he gradually improved and appeared to respond well to a psychotherapeutic approach. After discharge, he returned home and having to work in his father's business, his compulsions gradually returned. He moved away and improved, but his family joined him. Then, at the age of 22 years, he was again hospitalized for obsessional neurosis for some months and improved with largactil. He returned home, but was still unable to work. At 23 years he went to a Rehabilitation Unit. He could not cope and left. He remained at home and finally at 24 came to London and for a year he alternated between being a porter, a circus hand and a transport driver's mate. He has marked rituals, which he manages to hide. He feels freer and happier on the move. He would like to marry, but his illness, he feels, will prevent any girl getting fond of him.

Personality Disorder with Marked Obsessional Features

7. *Alan*. Admitted, aged 16 years, because of considerable withdrawal, inability to hold a job and a preoccupation with Underground train routes. His father had a history of

depressive breakdown; his mother, kind, dull and tenacious. Three younger siblings were normal. His early development was normal, except toilet training was not completed to 4 years of age. At school he was a poor mixer and was bullied. He was short-sighted, clumsy with his hands, and stuttered at one time. He was always slow and dreamy and his main joy was timetables and riding in buses and trains. He spoilt his work by attention to irrelevant details. He had been under the observation of a child guidance clinic from the age of 11 years. Latterly, he had been lying about and failed to make friends. He was of average intelligence.

He stayed in hospital for 6 months and became a bit more sociable. He resisted strenuous efforts in psychotherapy and remained preoccupied with abstruse geographical details. On follow-up, now aged 21 years, he has remained at home. Exceptional efforts had been made to get him to work, including a Social Rehabilitation Unit, without success. He has at last settled down in his uncle's firm, spraying and blocking hats. He mixes with no one, but goes to an art class. He has shown no interest in girls. He spends all his spare time in reference libraries, studying buses and trains. He collects maps and timetables and knows the routes and times of trains to anywhere. He is content and has no complaints.

Obsessive Compulsive State, with a Continuing Mild Tendency to Obsessional Rituals

8. *Pamela*. Admitted, aged 12 years, with a 2 years history, following her mother's miscarriage, of attacks of screaming and hostility to her mother. She became very slow, spent a long time in the lavatory and was difficult to get to dress or to undress. She had previously been treated in a child guidance clinic. Both parents were over-anxious and over-solicitous of this only child. She had shown no difficulties until her present illness. She was of low average intelligence.

In hospital, she had obvious obsessional rituals and she was timid and anxious. She improved, showed more initiative, mixed better and was for a time rather aggressive. She gained some insight in therapy into her relationship with her mother. She was discharged after 8 months, apparently free from symptoms.

At 19 years, she is a pretty and pleasant girl, still very attached to her parents. She has worked for 3 years in a drapery shop run by two maiden ladies. She spends her spare time bellringing, square dancing, with music lessons and churchgoing. She has made no real friends and refused the only boy who asked her out. She is rigid and noticeably mean. She is meticulous and has a very orderly life. If tense, for instance before her periods, she gets fidgety and opens and shuts drawers.

Obsessional Compulsive State with a Subsequent Normal History

9. *Graham*. Admitted, aged 12 years, with severe compulsive symptoms and ruminations of a year's duration, after being beaten up by a friend at school. His father had obsessional traits, his mother impatient and tense. A younger stable sister was mother's favourite. As a baby, he was a slow feeder and was clean and dry by 3 years. He cried a lot and thumbsucked up to 5 years. He was shy, a poor mixer, obstinate, overclean and tidy and very jealous of his sister. He was of average intelligence.

In hospital he gradually improved, and in psychotherapy he appeared to work through a good many of his difficulties. He was discharged after 17 months.

At 20, he still lives with his parents and there is now no disharmony with his sister. He remained at school to 15 and then became an apprenticed pastrycook, did well, specialized in decoration and won prizes. He is now in a job in Dusseldorf for a few months. He was rejected for National Service. He mixes well and has had one girl friend and now another. He is very clean and particular, but has had no further overt obsessional symptoms. A quiet and studious young man, who gets a bit concerned over minor ailments.

It seems from others' retrospective studies and from our small experience, that obsessional neurosis often starts in childhood or in adolescence. It tends to continue or to recur and there is also the question of the "obsessional personality". Is enough attention paid to prognostic implications in the study of these cases at an early stage by child psychiatrists?

PSYCHOPATHIC PERSONALITY

Children and adolescents with disorders of conduct, with or without accompanying neurotic disturbance are well known to child psychiatrists and to all other agents who deal with them. Most settle down as they grow up. Some do not, and child psychiatrists sometimes wonder which of these will later qualify for the title "Psychopathic Personality"? Much has been written about this term, but as time goes on there seems to be more uncertainty as to its nature. As Scott and Gibbens (14) have recently stated, "the main source of

difficulty in proposing a plan for dealing with the problem of the psychopath is the lack of knowledge—in definition, distribution, prognosis and treatment. We do not know enough about the nature of psychopathic personality to agree about a definition". This is not the place to dwell further on these difficulties. Most psychiatric discussion has revolved round adult psychopaths with their life histories in retrospect. At the other end, there is such valuable work as Bowlby's (1), on maternal deprivation and the concept of the "affectionless" child, and there has been the recent publication of a series of symposia held by the American Orthopsychiatric Association (10), in which an attempt was made to delimit the "psychopathic" child from other behavioural and neurotic disorders. The conclusions reached, however, by the participants were somewhat indefinite, and, as elsewhere, there was little attempt to link it up with the concept of "psychopathic personality" in adults. It seems that there is again much need for long-term studies of children into adulthood.

Many adolescents have been admitted to the Unit, boys more than girls, showing antisocial behaviour; and some severely delinquent. Admission was sought for a number of reasons; some required psychiatric investigation, others also showed neurotic symptoms or for some other reasons they were thought likely to be amenable to psychiatric in-patient treatment. Their symptoms, including the length of history back into childhood, and the 'problems that they presented, were most varied. As a group, they did not stand alone; they graded imperceptibly into those admitted because of neurotic syndromes. There was considerable overlap. Again, in personality, those with conduct disorders as a whole, when compared with neurotic children, did not appear to be more aggressive. One could not in any of them diagnose "Psychopathic Personality". In any case, much of adolescent misbehaviour is "psychopathic" or would be if it occurred in adults.

Fourteen patients (12 boys and 2 girls) aged between 12 and 16 years, had subsequently, by follow-up, aged 19 to 24 years, earned the title of Psychopathic Personality, bestowed on them in due course by one or more psychiatrists or prison medical officers. It is not proposed to discuss here the merits or demerits of this title in their cases. Such a diagnosis may have been correct, but its use appeared rather haphazard. Is this one reason why the term is so nebulous?

Be this as it may, examination of their records underlines that they were, as children and adolescents, a very mixed group. Ten other patients (6 boys and 4 girls) had in fact similar subsequent bad antisocial records, but they have not yet, as far as is known, been diagnosed as Psychopaths.

Examination of the records of the 14 so-called psychopaths shows that 1 boy was admitted with a neurotic condition. His antisocial behaviour supervened after discharge. Six others during admission showed neurotic conditions as well as conduct disorders. The other 7 were admitted with conduct disorders only; but some of them showed neurotic traits. During the first decade of the lives of this "psychopathic" group no clear-cut features distinguished them. However, an impression was gained that they were, as were the others with serious antisocial conduct, amongst those patients with the more unstable and disturbed family histories; they had suffered on the whole more than most patients from environmental disturbances in early childhood, but not particularly from maternal deprivation. By the second decade, they had become on the whole amongst the more incorrigible in their conduct and those most difficult for outside agents to handle. In the unit, most had relative difficulty in making positive relationships with the therapist or with other patients, but few

could be called "affectionless". Some appeared to settle down and to derive temporary benefit. On the whole, they were amongst the most awkward patients, although this was a matter of degree. In the majority, their antisocial behaviour continued and perhaps increased afterwards. There were, however, in contrast, at least 4 others, who, indistinguishable at the time of admission, had settled down and become more stable by the time of follow up. How many more will stabilize with increasing maturity? Here are some clinical examples:

Psychopathic Personality

10. *Keith*. Admitted, aged 16 years, following a charge of indecent interference with small girls. Both parents were strict and unaffectionate, there were 2 younger normal children. His early development was normal, but from 5 to 8 years he was evacuated to a strict family. He was always quiet and solitary and latterly he had been sullen, bad tempered and seldom went out. The sexual interference then occurred. He had been masturbating excessively.

A shambling, miserable and guilty youth of high average intelligence and with a normal EEG, he was passive and unco-operative in psychotherapy. After 2 months, he repeatedly absconded and finally stole a motor cycle, which led to committal to an approved school. He appeared to seek punishment and stated he would rather be in Borstal than talk of his sexuality.

He went on to abscond repeatedly from the approved school and was again apprehended for sexual interference with girls and sentenced to 18 months imprisonment. After discharge, he returned home, now aged 20 years, and was at once sentenced to 4 years for raping a girl. After discharge, he was again sentenced to 4 years for attempting to rape a 57-year old woman and for possessing an offensive weapon. He is regarded as a psychopath and castration has been requested by him and advocated by psychiatrists.

Psychopathic Personality

11. *William*. Admitted, aged 12 years, because of violent tempers since the age of 7 years, for which he had attended a child guidance clinic and then been admitted as maladjusted to two schools, but had absconded. He had had an eye removed at the age of 1 month and was very conscious of his glass eye. The father was an anxious disciplinarian, with many somatic complaints; the mother anxious and emotional. Both were over-protective, upset about his eye and feared to have another child. His early development was normal, but lately he had been having nightmares. He was of dull intelligence and had an unspecific, abnormal EEG.

In hospital he was superficially co-operative, but seemed actively afraid of failure and generally resentful. There was a strong undercurrent of hostility. Strenuous efforts were made to deal with his problems in psychotherapy, but he repeatedly absconded and finally got himself arrested and charged as beyond control and committed to an approved school. He was later discharged as unlikely to benefit from training. Aged 18 years, he was placed on probation for stealing and a few months later he was in Court for being drunk and disorderly and again for throwing milk bottles. He had had many jobs or avoided work. His tempers were severe and his parents in terror of them. Again, he was in Court for inflicting grievous bodily harm and admitted to a mental hospital. Here he was diagnosed as a psychopath. He settled down for a time and then became restless and was discharged. He had by now got his girl friend pregnant. This is his career up to date. Further details of his symptoms and personality are not known.

Psychopathic Personality

12. *Peter*. Admitted, aged 13 years, for truancy, stealing and stammering. His mother was inadequate, anxious and asthmatic; with minor fits in the past and a history of hospital treatment for recurrent depression. Peter was illegitimate. The stepfather "picked on" the boy. They lived in a very restricted flat. A breech delivery after a long and difficult labour, he was bottle-fed and had much vomiting. He also had repeated convulsions. At 3, he reacted with nightmares and enuresis to his stepfather joining the Army. At 4, his home was bombed and he was evacuated to 6 billets in 2 years. At 5, stammering began and also wandering. At 6, he and his mother were trapped in a train that was bombed. He was very frightened and became disobedient and destructive. He was treated in a child guidance clinic. He improved, but his mother went to hospital and his stepfather returned. His symptoms recurred and he stole from his stepfather. He now attended the Maudsley Hospital Children's Department, on and off for 3 years until admitted. He was now also educationally retarded, aggressive and mischievous. He had an abnormal EEG focus in the temporal region. He was of average intelligence.

In the adolescent unit, he was active and mischievous. At first very anxious, he responded well to the hospital régime, a psychotherapeutic approach and amphetamine. After 7 months, he was sent to a residential school for maladjusted boys, where he remained until 16 years. He gave no particular trouble. He returned home to a more spacious new house, and did a number of unskilled jobs. He was now twice charged with larceny, put on probation and at

18 years volunteered for the Army. He was discharged as a "psychopathic personality" after stealing, aged 20 years. He was next sentenced to Borstal for further stealing. Interviewed at 22, he was a good-looking, plausible young man with a slight stammer. He was free from neurotic symptoms and his EEG was now normal. He had girl friends and liked the good things of life. He intended to settle down and make good. A month later he was again charged with stealing.

Severe Behaviour Disorders in Childhood, which Settled Down

13. *James*, Admitted, aged 16 years, because of inability to hold a job, truancy, petty thieving, temper outbursts and lying. His father had a duodenal ulcer; his mother, an aggressive, voluble woman had little affection for James. A number of relatives were unstable. His two younger brothers, however, were stable. He suffered a birth injury and was cyanosed for 2 days and then developed septicaemia. A troublesome babyhood, with vomiting, failure to gain weight and much crying. After his brother's birth he became, according to his mother, "the biggest devil". He was aggressive, disobedient and a liar. At 8, he attended a child guidance clinic for a time for fidgeting, stammering and disturbed sleep. Later he attended another child guidance clinic. He went to 6 schools, got on badly with lessons, had few friends and was often in trouble. He then held 6 jobs in 2 years, joined the Army and deserted. He was already diagnosed by some as a psychopath. He was admitted because he had walked into a river.

He was found to be of average intelligence and an EEG was mildly abnormal. He stayed in hospital for 5 months and remained childish, unstable, mischievous and without persistence. He was tense and hypochondriacal. He improved somewhat with psychotherapy directed towards sorting out his family inter-relationships.

After discharge, he quickly reverted to his previous state and a year later was admitted to a mental hospital twice for some months. He was diagnosed as a schizoid psychopath. He remained childish and aggressive. At 19, he was committed to Borstal for breaking and entering. He was discharged, aged 21, and settled down in a regular job. He is now aged 23, belongs to a club, has a full social life and is interested in singing. He has many friends and has been engaged. He appears to have entirely changed and while at Borstal saved the life of an officer. He is symptom-free.

Severe Conduct Disorders in Childhood, which May Now be Settling

14. *Richard*. Admitted, aged 13 years, for stealing and aggressive behaviour, which led to his exclusion from a residential school for maladjusted children. His father was a martinet and his mother anxious. Neither could control their 6 children; 3 of whom had attended child guidance clinics or been in Court. His early development was normal, but after his return from evacuation, aged 6, he was showing night terrors, sleep-walking and a number of neurotic traits, including enuresis. So disturbed was he that he was admitted for 9 months to the Children's In-patient Department of the Maudsley Hospital. He improved, returned home and soon showed acute conduct disorders with 3 Court charges and with increasing educational retardation. He again attended a child guidance clinic. He then went to a boarding school for maladjusted boys for 2 years until excluded. He was of average intelligence and his EEG was normal.

In hospital, he settled down well, but bullied the smaller boys. He was mischievous and destructive. After 2 months, he absconded, stole a motor cycle and was sent to an approved school, where he remained until 16 years old. His enuresis now cleared up. He had many casual jobs in the building trade.

He was charged a number of times for petty thieving and driving away cars. Aged 17 years, he was sentenced to Borstal and was discharged at 19 years. Soon after he was charged with loitering with intent, but this was dismissed.

At 19, he has no overt neurotic traits; he has kept one job for 3 months since leaving Borstal and is getting on better with his family. The other children have all settled down, although one is still in an approved school. He is not particularly interested in girls and enjoys a mild social life. He hopes to join the Army and drive army lorries. He is likeable and immature. He may be settling down and has not yet been diagnosed by any psychiatrist as a psychopath.

To sum up: it is apparent that nothing definite is here contributed towards the elucidation of the difficulties raised by the concept of Psychopathic Personality and its unfolding in the maturing child, although our experience points to its heterogeneity. Once again, it seems that prospective clinical studies of such children by child psychiatrists, who have detailed knowledge of their early lives and circumstances, may bring some reward.

CONCLUSION

This address has kept deliberately to the sometimes neglected subject of clinical psychiatry in children. It has ignored psychopathological concepts and it has omitted the important ties that Child Psychiatry has with Paediatrics, with Psychology and so on. Time has not permitted discussion of many other threads which bind Child Psychiatry to the fabric of Psychiatry as a whole. However, it is of interest that Mayer-Gross and Slater (11) in their textbook *Clinical Psychiatry*, now include together in one chapter "Psychopathic Personality and Neurotic Reactions". How far their inclusive approach is acceptable is a matter of conjecture; it is certainly appropriate and a relief to apply their concepts to the very mixed syndromes to be seen during the second decade.

Finally, the training of child psychiatrists is at present under consideration, with an emphasis on recruitment. Creak (6), in the Charles West Lecture of 1958, dwelt on the pressing need of paediatricians for knowledge and training in the psychiatry of children and discussed the means by which they can get this or sometimes turn over to become child psychiatrists. Recently, Tizard and others (15) wrote on the same theme. Such is welcome, although this follow-up material demonstrates, if it does nothing else, that adequate knowledge of the clinical psychiatry of adults is most necessary for an appreciation of the long-term implications of psychiatric ill health in children; and this is apart from the proper understanding of the psychiatric ill health of parents, who are also the concern of the child psychiatrist. It would thus seem important that the training of the child psychiatrist should continue to provide for this aspect of their work and that it should also not be ignored by paediatricians.

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THE MOOD-PROJECTIONS OF WALT RUHMAN

By the late

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IN these days we expect a good deal of a painter with claims to originality—a good deal more than most of them can give. We are habituated to pictorial representation as a major means of communication of ideas and we are surrounded by technically proficient work in the competitive field of advertising. Work of this kind is evocative too—at least to the variety of emotions which may determine the act of buying—and the poster that does not come off soon comes down. Except in the esoteric field of prestige-advertising, the sales-curve is the sole judge of the efficacy of this kind of appeal and the consumer—the indirect and unwilling patron—is rarely himself able to judge the effects of such hidden persuaders as the artist has built into his work.

When it comes to the assistance which art can give to man in realizing his spiritual and intellectual potentialities, there is no statistical guide to success and his own biased testimony is all we have to go on. Even so, one can come away from an exhibition angered, uplifted or indifferent, but without really knowing what has been its impact on less conscious elements of the mind, or the extent to which it has altered one's basic attitudes. A painting will occasionally inspire at a glance, but more telling are those which are able to pass the barriers of consciousness and rationalization. Civilized man has erected these defensive barriers mainly against a verbal assault, so that artistic presentation can occasionally penetrate the emotional life when mere words fail to do so. But this can be achieved in the case of painting only if the initial impact and the technical quality of the work is such as to attract and hold interest and if it can excite a response by its own rhythm, vitality and form. It must be able to draw the eye to its artistic and thence to its spiritual meaning. We thus expect of a painter that he will have command of the medium as well as a message worth transmitting or a feeling worth expressing. If a painting can make us think, determine a change of attitude and even add something to the art form then we may, if we can comprehend its language, accept it as creative. It is by these acting standards that we must judge the work of Walt Ruhman, for his aim is at once to express his feelings, to communicate to us his misgivings about civilization as he finds it, and to make his contribution to the language of his chosen medium.

In the spread of new ideas, art finds its place as the language of feeling. Just as the Zen Guru, setting all ritual and visual influence aside, uses his *koans* and paradoxes as mental devices to bring him to the threshold of enlightenment, so the artistic paradox, the well-timed visual question-mark, may sometimes enable us to see beyond our immediate circumstances. No one would deny that Walt Ruhman's work is full of question-marks, but can he also satisfy us as to his fluency in this form of non-verbal communication? This we can only decide as individuals by our reaction to his work. (See Fig. 1.)

What are his qualifications for undertaking the task he has set himself? Ruhman is a doctor, a physician with a full but interrupted medical career, one of those people who share with the competent in his own and other fields the common qualities of the competent man. He is also a man of enthusiasm and it is this continuing drive which has impelled him to paint over a period of almost fifty years. Most of his life has been devoted to medical work, and medicine in its turn has given him the intimate knowledge of mankind in distress which is so evident in his work. The humanity he has encountered has left its mark on him and while in some of his work he is expressing and acting out his own feelings and drives, he is unmistakably identified with humanity as a whole—for humanity is his subject. There is no question of Ruhman being unsophisticated, for even his childhood work is far from naïve (Fig. 2). As one follows his painting through the years one can trace his deep interest in the development and in the language of painting. There is nothing carefree about his work and its clean lines, its confident use of curves and spatial positioning, speak of the planning and complexity of intent which lie behind it. It may take a little time before "the penny drops" when one is looking at some of Ruhman's paintings of "The Age of Trial" series, but it is in this period of gloomy commentary that the great intensity of his work is most evident.

The marked contrast between the different periods of Ruhman's artistic life indicates a man of moods. That he can feel strongly and identify himself with an ideal is testified by his devotion to the group of Pastor Niemöller which led to his leaving Germany. As a refugee and an internee in this country and in Canada he knew what it is to be one of the many—an *untermensch*—to be "messed about" on the side-lines of a great social explosion, and in his satiric pictures there is a great deal of healthy underdog humour. His own face among his groups of contemporary types shows that in his happier moods he can participate and he is seen as very much one of the crowd, in contrast to the detached prophet of gloom in his "Age of Trial" series.

In 1938 Ruhman left a full professional life in Berlin for one of mere existence and had then to rehabilitate himself in a new culture. It is not to be wondered that from his medical interest in sick people he was led to a consciousness of sick societies and it is fortunate that he has always had with him a biographer of his moods and fortunes, for he began to draw as a child and learned early on to express his feelings through his brush. He refers to his work as *expressional*, and for him the word has a special meaning. When he is in a state of tension it has a cathartic quality, cathartic in the sense both of the Greek tragedians and of contemporary psychopathology. At these moments his work has been his outlet and his protest. Although he may desert realism in pictorial representation, there is nothing unreal about the emotions which he communicates, and in this sense his treatment can be regarded as one of realism in the emotional sphere. Some of the special appeal of his work is that it is a product of an emotional state the nature of which he is able to communicate to others by touching in them a resounding chord. He is an affective realist.

Although his work has psychiatric significance, it needs little psychiatric interpretation, for its language is simple and universal. It is a common error in these times to regard painting which exploits the unreasoning qualities in human perception as necessarily having something in common with the disordered thought of the schizophrenic. Examination of Ruhman's paintings from this point of view yields little evidence of such thought-disorder and there is only one piece which has any quality of this kind at all—this is the face which he drew at the age of fourteen (see Fig. 3), an age when few of us are without a little



FIG. 1 —Gaspard, Oil, 1944



FIG. 2.—*The Sculpture*. Colour ink, 1956.



FIG. 3.—*The Devourer of Nations*. Water-colour at age of 14.



FIG. 4.—*The Slum Porch*. Oil, 1949.



FIG. 5.—*Heritage*. Oil, 1943.



FIG 6.—*Mid-Century Dawn*. Oil, 1946.

disordered thinking and some uncertainty and torment are to be expected in the intelligent and sensitive. In Jung's language, Ruhman from his pictures would be the relatively rare type of feeling, intuitive extravert.

Sometimes when an individual with a sound technique and background of expressing himself in painting is the subject of a severe psychosis, the work he produces is thought-provoking and way-pointing, as is the work of an efficient and gifted mind under stress and in torment under the threat of breakdown. In such periods of distress unconventional associations of ideas may achieve a break-through in pictorial expression which is ahead of its time, so that the psychopathic art of one generation may anticipate, in some features, the expressionist and abstract art of the next. The psychotic, with notable exceptions, is usually unable to exploit his advances. The creative artist on the other hand may be eccentric but in relation to his work his qualities have as much the qualities of brilliance rather than of insanity, for he retains some contact with the world which is to judge his work. To succeed, he may have to believe in what he is doing at the time to the subordination of all other duties, and this may render him a misfit. But there is little of the misfit about Ruhman, and when he is not being a prophet of gloom on canvas, his adaptation to life is first-class. The energy and single-mindedness necessary to accomplish any work of creation may itself come from abnormal resources and over-valued emotions, but this is not to say that they cannot come from a healthy mind which knows how to exploit such unreason as he finds available in himself. The idea that truly creative work must necessarily come from psychopathic sources is ill-founded and it is this belief that has encouraged the amateur bohemians who feel that they must experience the decadence of Toulouse-Lautrec, the catastrophic moods of Van Gogh and the provocatively anti-social escapism of Gauguin before getting into production. In Walt Ruhman we find some vindication of the opposite view, for he is a sociable man and in contact with his fellow creatures, can use his leisure and likes his work. He has not been cast down by his experiences, yet he can portray bitterness as well as any paranoiac (Fig. 4). It is surely unnecessary to have melancholia to play Hamlet. It is better to be a competent actor who can identify himself completely with the part for the evening. The strength of Ruhman's work is in its identification with an emotional state.

When something new in painting makes its appearance, it is customary to try and trace its origin in the work of others, for the technique and intuition of a painter has necessarily to be made up of the influences he has encountered together with the synthesis which is his own and which expresses his individuality. It is not relevant to their purpose to say that in looking at these pictures one is reminded, as one inevitably is, of the distorted human forms of Bosch, the caricatures of Daumier, the painful realism of Goya, and the mysticism and stylizations of Blake and the plastic rhythm of the Mexican moderns, though influences such as these are certainly there. It is more rewarding perhaps to regard the pictures in longitudinal section through Ruhman's life and to leave out the academic exercise of tracing the sources of his technique. The mood-salad of pictures which portrays his life has some fascinating ingredients, some too strong for the average stomach. We see the artist at different stages of development and identified with different moods and causes. We see him downcast and taking the troubles of the world on his shoulder, we see him as a caricaturist of acute perception, and sometimes we see him self-conscious and failing to carry conviction, but always an observer of the social scene.

Where his personal biography has been representative of our times and its problems he is at his most convincing. "Heritage" is perhaps his most telling and by itself justifies his efforts (Fig. 5) and "Mid-Century Dawn" (Fig. 6) brings us up against realities—the squalid realities of the mass-mind and its disregard for humanity. As a poster for an anti-nuclear war campaign it might carry conviction where the appeal to pure reason fails by its obviousness.

Looking at "Heritage" we are impelled to ask why does this man-child crouch in the ruins of his world in the manner of a child in the womb, in fear and uncertainty, trying to shut out from his mind the realities all about him. The picture does a good deal more than exemplify the mental mechanisms of regression and repression; it is more even than a romantic portrayal of human disaster on a nuclear scale. This creature is both the artist and ourselves, ambivalent as to whether to go on or fall back afraid, sick in body, numbed, yet preternaturally clear in mind. His intelligence has been brought to naught by the failure of civilization to take man's individual nature into account and by the excesses of the uncontrolled group-mind. We are left with the question-mark—will civilization fail us? Ruhman's work is full of such unanswered questions. It may take time to assimilate this most original of spare-time painters, this sane exploiter of the unreasoning mind's eye, but neither his work nor the questions it asks can be ignored.

DRUGS AND PERSONALITY

VI. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS UPON BODY SWAY (STATIC ATAXIA)*

By

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1. INTRODUCTION

IN a previous study H. Holland (3) had found an increase of static ataxia under a depressant drug, as compared with a "no drug" condition, and in view of the close relation between static ataxia and the body sway test of suggestibility (1), which in turn is a frequently used measure of personality, it appeared desirable to investigate the general problem of the relation between drugs and behaviour on the ataxia test.

2. THE EXPERIMENT

(a) *Drugs*

D-amphetamine sulphate (5 mg.), sodium amylobarbitone (90 mg.), meprobamate (100 mg.), and a placebo (225 mg. lactose) were packed in identical capsules. Three capsules of the chosen variety were administered per day, two in the morning and the third with an extra placebo capsule four and a half hours later, an hour after lunch. The incubation period allowed for each drug ($\frac{1}{2}$ hour for all but amylobarbitone which was 1 hour) was occupied in the morning by the collection of biographical data and in the afternoon by casual conversation. Testing was completed in an hour and a half. The subjects were requested to restrict their intake of tea or coffee at breakfast and were denied either at lunch.

(b) *Experimental Design*

The experimental design, a balanced incomplete block, ensured that each drug would be given once after each other drug and in each serial position as shown in Table I. The block was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion here was only one of several applied to the same group of subjects under identical conditions; the other tests will be discussed in later papers. The body sway test was the fifth to be carried out.

* We are indebted to the Wallace Laboratories for the support of the investigation.

† Now at the Burden Neurological Institute, Stapleton, Bristol.

TABLE I

Experimental Design: Treatment Given on Day Indicated to Indicated Subjects

Subjects		Days			
Block I (a.m.)	Block II (p.m.)	1	2	3	4
1	2	A	B	C	D
3	4	C	A	D	B
5	6	B	D	A	C
7	8	D	C	B	A

A=Placebo, B=Amphetamine, C=Amytal, D=Meprobamate.

(c) Subjects

The subjects were five men and three women members of a club that limits its membership to those who can make high scores on a paper-and-pencil test of the intelligence test type. Their behaviour seemed as alert and ego-involved as this fact suggests.

(d) Method of Measurement

Body sway in the forward-rearward direction was measured against the movement of a spring-loaded wheel from a neutral position as a result of the increase or relaxation of a slight tension on a string between the wheel rim and the subject. The string was clipped to a belt around the subject's chest, or to his collar if it were tight. The apparatus yields three readings: (a) the difference between the extreme positions reached in forward and rearward sway, (b) the total number of alternations of direction of sway, and (c) the total number of times a given point on the wheel rim moved through a (short) unit of distance, which is an index of the total amount of movement.

3. RESULTS

The mean scores for body sway are presented in Table II. Analysis of variance of the raw scores showed three of the matrices whose means are

TABLE II
Body Sway Scores

				Treatments			
				Placebo	Amphetamine	Amytal	Mepro- bamate
<i>Mean Scores in Arbitrary Units:</i>							
1. Difference between extremes:							
Eyes open (EO)				1.08	0.89	1.48	1.13
Eyes closed (EC)*				1.42	1.19	2.29	1.18
2. Number of alternations (EO)*				6.25	6.37	13.12	10.00
(EC)				9.87	11.87	16.62	14.25
3. Total movement (EO)*				4.75	4.37	9.75	5.62
(EC)				8.37	10.12	15.87	9.37
<i>Means as Percentage of Individual Totals:</i>							
1. Difference between extremes (EO)				19.4	17.9	39.8	23.0
(EC)				19.2	23.1	36.3	21.4
2. Number of alternations (EO)				17.5	17.8	36.7	28.0
(EC)				18.3	22.1	30.9	28.9
3. Total movement (EO)				23.6	19.5	32.3	24.7
(EC)				23.4	19.5	37.5	19.3
Average of percentage scores*				20.2	20.0	35.6	24.2

* Significant by analysis of variance.

shown in Table II to be significant. These were: the difference between extremes with eyes closed, alternations with eyes open, and total movement with eyes open. As shown, all other means indicate comparable effects. Thus the matrix of mean percentage scores shown in the table is highly significant ($F=36.9$ with $3/20$ d.f.). The standard error of the difference between any two column means in this matrix is 1.7 , so that performances under both amylo-barbitone and meprobamate treatments are significantly less accurate than those under the placebo or amphetamine treatments.

4. DISCUSSION

The results leave little doubt that depressant drugs have three effects. They increase the amount of forward and backward sway; they increase the number of alternations (swings forward and backward); and they increase the total amount of movement of the subjects under the conditions of the test. The stimulant drug used showed a slight tendency in the opposite direction, but this was so minute that it is doubtful if the finding could be duplicated. For all practical purposes, amphetamine in the dose administered had the same effect as the placebo. Of the two depressant drugs used, amylobarbitone was more potent, in the dosage used, than was meprobamate.

Many hypotheses could be advanced to account for these results. It may be possible to link up the findings with the general theory of excitation-inhibition (2) along the following lines. The maintenance of body posture requires a constant adjustment of the relevant muscles in line with information supplied by the eyes (when open), by muscle spindles acting as interoceptors, etc. These perceptual and motor activities are subject to satiation (reactive inhibition), and as satiation is stronger in extraverts than in introverts, and is increased by the administration of depressant drugs, we would expect performance to be worse in extraverts than in introverts, and in subjects administered a depressant drug as compared with those administered a stimulant one, or a placebo. As regards personality, static ataxia has been shown to correlate with neuroticism (1), but nothing is known concerning its relationship with extraversion. As regards the drug effects, the results are in line with prediction, excepting that the favourable effects of stimulant drugs, which ought to decrease satiation, are not very apparent.

A possible test of the hypothesis here put forward would be this. Reactive inhibition requires time to accumulate, and consequently it would be expected that if the total period of static ataxia measurement were to be divided up into 10-second intervals, then placebo and drug conditions should become more unlike each other during successive intervals; in other words, there should be a drug-trial interaction. No repeated measures were taken in this experiment, and consequently no data are available to prove or infirm this hypothesis. It might also be postulated that reminiscence effects should be greater for extraverts and subjects administered depressant drugs; it is not known whether this prediction would be borne out in fact. In view of the general significance of static ataxia in medicine and in psychology, further work along these lines might be of some interest.

5. SUMMARY AND CONCLUSIONS

The effects of d-amphetamine sulphate, sodium amylobarbitone, and meprobamate were compared with those of a placebo in respect to their power to influence subjects' static ataxia. It was predicted, on the basis of Eysenck's

drug postulate, that depressant drugs should increase static ataxia, while stimulant drugs should decrease it. The first prediction was verified at an acceptable level of statistical significance; the second prediction was not verified, results supporting it too slightly to infirm the null hypothesis.

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DRUGS AND PERSONALITY

VII. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS UPON PUPILLARY REACTIONS*

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1. INTRODUCTION

THERE has been relatively little work in psychology and psychiatry in which use has been made of the pupillary reaction to light and darkness; most of the work that has been done has been connected with the relatively slow reactions found in schizophrenia. This neglect is difficult to understand in view of the fact that this reaction and the autonomic innervation determining it are relatively well understood and do not present the same experimental and theoretical difficulties as the psychogalvanic reflex which is very much more widely used (Martin, 1960). In the present study, which forms part of a larger series, an attempt was made to investigate the influence of drugs on the reactivity of the pupil to changes in light stimulation.

2. THE EXPERIMENT

Details of drugs, experimental design and subjects have been given in a previous paper (Eysenck and Easterbrook, 1960). Eight subjects in all were tested under four drug conditions (d-amphetamine sulphate, sodium amylbarbitone, meprobamate, and a placebo), under an experimental design which ensured that each drug would be given once after each other drug and in each serial position. The experimental design, a balanced incomplete block, was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion here was only one of several applied to the same group of subjects under the same conditions. This test was the sixth to be carried out, immediately following the body sway test discussed in the previous paper.

The subject was seated in a flood-lit position with his head clamped in front of a cinecamera which was focused on the pupil of his left eye. A six-volt, twelve-ampere bulb was arranged to shine down a tube into his right eye, which was shielded from outside stimulation. After two minutes adaptation to the flood-lights, S was warned to fix his vision on a spot on the camera face, and records were made of left pupil size during (a) a period of five seconds when the right eye was unstimulated, followed by a period of twenty-five seconds with the stimulus "on" (contraction series), (b) a period of five seconds with the

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† Now at the Burden Neurological Institute, Stapleton, Bristol.

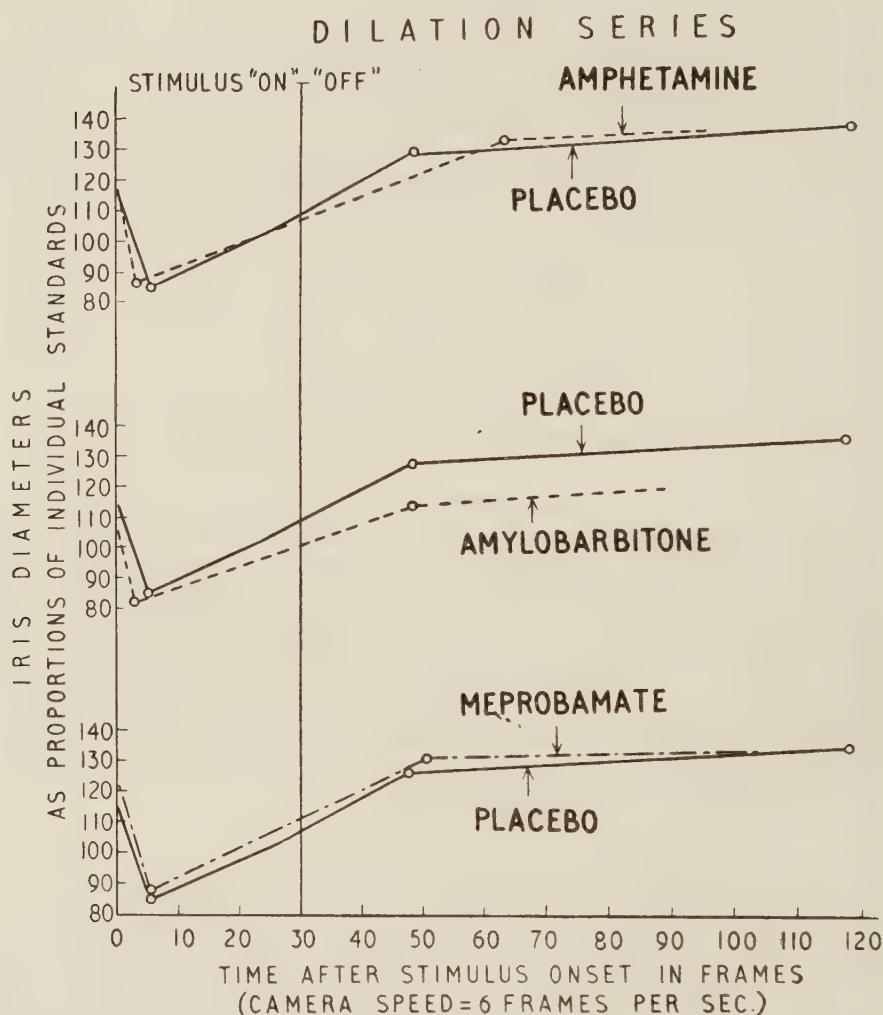


FIG. 1A.

stimulus "on" followed by a period of twenty-five seconds with the stimulus "off" (dilation series), and (c) a series of twenty-five cycles in each of which one second of stimulation was followed by four seconds without. The film was subsequently projected at an enlargement of about twenty to one on to a ground glass screen and iris sizes were measured with calipers automatically feeding their settings into a recorder. The following readings were then taken: (i) initial diameter, (ii) minimum diameter after stimulus onset, (iii) maximum compensatory dilation within five seconds of stimulus onset, (iv) the first subsequent diameter not exceeded for fifty frames, (v) the final maximum diameter, i.e. the largest size reached during the whole of the experiment, as well as the time in frames between each incident.

CONTRACTION SERIES

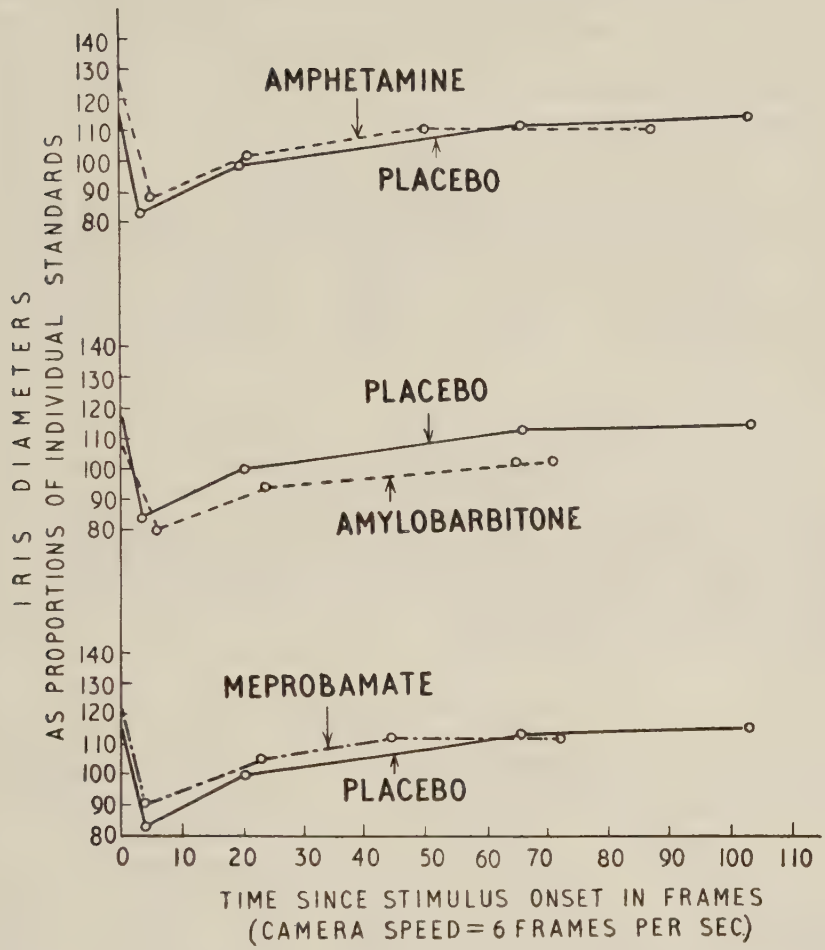


FIG. 1B.

3. RESULTS

(a) Iris Size Response to Stimulation

In both the "contraction" records and the "dilation" records the iris contracted rapidly to a minimum within 2-6 frames of onset of the stimulus, and then showed a compensatory dilation with cyclic variation to a maximum. During the first five seconds with stimulus "on" the data duplicated one another, so it was possible to estimate the test-retest reliability of the measures. Using a coefficient of consistency* on the readings of maximum compensatory dilation within five seconds of stimulus onset (which were to serve as standards—see below), the consistency of the scores was found to be sufficiently high ($r_c = .988$) to justify considerable reliance on these data as read.

* $r_c = 1 - V_{sb}/V_{sw}$, in which V_{sb} signifies the variance attributable to subjects between replications on the same subjects and V_{sw} signifies the variance attributable to subjects within replications.

The mean iris diameters at the point of maximum compensatory dilation within five seconds of stimulus onset for both the "contraction" and the "dilation" records under the different treatments are shown in Table I (see also Figs. 1a and 1b). In these data, the effect of drugs is significant when tested against the replication variance ($F=14.0$ with 3/3 degrees of freedom (d.f.)). The meprobamate treatment produced the largest and the amytal the smallest iris diameters.

TABLE I
Mean Iris Diameters in Millimetres
At Point of Maximum Dilation Within Five Seconds after Stimulus Onset

	Treatments			
	Placebo	Amphe- tamine	Amylo- barbitone	Mepro- bamate
"Contraction" records ..	1.450	1.480	1.355	1.517
"Dilation" records ..	1.470	1.460	1.347	1.475

The mean for each subject was calculated from the eight available measures of iris diameter at the point of maximum compensatory dilation (within five seconds of stimulus onset). There are eight measures on each subject because there are 4 conditions $\times$ 2 series. All other readings were then converted to ratio scores, using these means as 100, and subsequent tests were made with the data in this form. Table II shows the means for each treatment of these ratio scores at each point at which readings were made. The pattern of treatment effects confirms that noted in Table I.

TABLE II
Mean Iris Diameters
As Percentages of Individual Standards Taken at the Point of Maximum Compensatory Dilation Within the First Five Seconds After Stimulus Onset

	Treatments			
	Placebo	Amphe- tamine	Amylo- barbitone	Mepro- bamate
<i>Contraction Records:</i>				
Pre-stimulation	116.9	125.5	107.5	123.0
Minimum with stimulus "on"	83.9	86.9	81.1	89.9
Maximum in 5 seconds after stimulation	99.7	102.4	93.9	105.5
First true maximum*	112.6	111.0	102.4	111.7
Grand maximum*	114.9	112.5	102.7	112.2
<i>Dilation Records:</i>				
Pre-stimulation	114.9	118.4	106.9	122.6
Minimum with stimulus "on"	84.9	86.5	81.9	87.5
Maximum in 5 seconds after stimulation	101.7	100.9	93.0	102.1
First true maximum†	127.5	132.5	114.4	131.4
Grand maximum	135.0	135.0	118.6	134.4
Means	109.20	111.16	100.24	112.03

* The "first true maximum" was defined as the first maximum diameter after stimulus onset that was not exceeded for 50 frames (8.33 seconds). The "grand maximum" was the largest iris diameter observed in the record.

† In the dilation records the stimulus had been turned off after five seconds.

Two points may be made about the calculations in Table II. First, in the absence of the light stimulus (i.e. in the "dilation records") the grand maxima

for the placebo, amphetamine and meprobamate treatments may be the same. Second, despite this, the averages of all treatments but amphetamine and meprobamate differ from one another at the .01 level of significance, so that there is a general effect of treatments on iris diameter.

(b) Iris Responsiveness

The changes in iris diameter in Table II are responses to stimulation or to withdrawal of stimulation. The speeds at which such changes occur are indices of responsiveness in some sense to stimulation or to withdrawal of stimulation and are likely to have fundamental importance. The matrices of time lapse between the points at which readings were taken showed no significant relations to treatment; calculations were therefore made for each individual of the net amount of change between adjacent points per unit time difference (in frames). Table III displays these mean rates of change under each treatment, with two related calculations.

TABLE III
Net Change in Iris Size Between Reference Points
 (Unit averages .44 mm./seconds)

Reference Points From-To	Treatments			
	Placebo	Amphetamine	Amylo-barbitone	Mepro-bamate
Stimulus onset–minimum	–7.88	–9.10	–6.09	–7.42
Minimum–C/maximum in 5 seconds*	1.03	0.96	0.69	0.87
Total change in 5 seconds	8.91	10.06	6.78	8.29
C/maximum in 5 seconds–1st true maximum with stimulus “on”	0.280	0.309	0.209	0.282
C/maximum in 5 seconds–1st true maximum with stimulus “off”	1.100	0.795	0.875	0.934
Difference off–on	0.820	0.486	0.666	0.652

* Compensatory maximum within the first 5 seconds after stimulus onset.

The data in Table III suggest that two dimensions underlie the differences between treatments in speed of change of iris diameter. The first is clearly *responsiveness to stimulation*, indicated by the contraction “rates” (amylo-barbitone reduces responsiveness and amphetamine increases it). The concomitance of the mean rates of compensatory dilation (stimulus “on”) with those during contraction suggest that the rates of compensatory dilation (stimulus “on”) vary directly with the rates of contraction to the stimulus. In more general terms *negative adaptation* (or “habituation”) to this stimulus seems to proceed more rapidly when *sensitivity* to the stimulus is greater. However the rates of dilation with the stimulus “off” that are shown in Table III are not apparently related to the rates of compensatory dilation. (All drugs retard this, as compared with placebo.)

None of the matrices whose means are displayed in Table III showed a significant effect of drugs when analysed individually, although the differences between amphetamine and amylobarbitone in total change in the first five seconds and in the rate of compensatory dilation (stimulus “on”) are significant by t test. Nonetheless the effects seemed to present a pattern.

A new 8×4 matrix was therefore composed using the means for each of the two groups of four subjects that composed a block, of the following

measures: rate of contraction, rate of compensatory adaptation within the first five seconds, rate of compensatory adaptation to the first true maximum (stimulus "on") and the total (without regard to sign) of the first two slopes ("total change in first five seconds"). Thus we are using averages of 4 indices of responsiveness to stimulation. Each of the treatment means on these measures was expressed as a percentage of the total across treatments, so that the four indices became comparable and could be averaged. The mean percentages obtained were: placebo, 26.8; amphetamine, 29.1; amytal, 20.1; and meprobamate, 24.0. This matrix shows a significant drug effect ($F=10.0$ with 3 and 18 d.f.) and t tests of the difference between adjacent means ($SE_d=1.72$) showed all differences except those between the placebo and either meprobamate or amphetamine to be significant (at $P=.05$).

A similar large matrix could not be composed to test the observation that the rates of dilation after cessation of stimulation (and the difference of these rates from those for compensatory dilation) may reflect a second dimension of difference between treatments. However, this possibility cannot be confidently rejected. The difference between the scores for placebo and amphetamine treatments in the "Difference Off-On" (whose means are shown in Table III) yields a t of 2.09, while a t of 2.12 would be significant at the .05 level of confidence.

(c) *Effects of Repeated Stimulation*

The records which had been made of the changes in iris diameter during the period of two minutes when 25 one-second flashes of light were presented at regular intervals revealed no indication of differences between treatments beyond those of general iris size. The records themselves were imperfect, due to a great number of long blinks or winks. These cases of lid closure were apparently bilateral and affected the phenomenon under investigation by interrupting the stimulation. In several records the lid closure coincided with the stimulus onset quite neatly. The repetition of short flashes of light seemed to produce a higher incidence of lid closures than did the continuous stimulation, particularly under the three drugs.

4. DISCUSSION

The results reported above leave no doubt that the drugs used strongly affected the response of the pupil to light stimulation and its recovery. Responsiveness to stimulation is quickly retarded by the depressant drugs, particularly amylobarbitone, as compared with placebo conditions; it is increased by amphetamine as compared with placebo conditions. It appears at the same time that negative adaptation (of the contraction response) is most rapid under conditions in which sensitivity to the stimulus is greatest, i.e. under stimulant drugs, and proceeds more slowly under conditions in which sensitivity to the stimulus is least, i.e. under depressant drugs and particularly under amylobarbitone.

The data suggested that in addition to this pharmacological effect in responsiveness to stimulation (or sensitivity) there was also present another factor related to rates of dilation with the stimulus off. This type of dilation appeared to be retarded by all the drugs but most of all by amphetamine. In view of the border-line significance of this finding we cannot be sure that there does in fact exist a second dimension of this type in the data, and a repetition of the experiment would be necessary before any certain conclusion could be

arrived at. However such an investigation might be eminently fruitful. A single line of behaviour—pupil dilation—is here manifestly sensitive to both continuation and cessation of stimulus energy, and it is the suggestion of these data that its two hypothetical mechanisms are differently affected by drugs.

Our main interest from the theoretical point of view had lain in the effects of repeated stimulation because it would be predicted from the drug postulate, which was outlined in the first paper of this series, that adaptation to repeated stimulation (inhibition) should proceed more rapidly and more strongly under depressant than under stimulant drugs. The large number of eye-blinks elicited by the testing procedure makes it impossible to use the data in any definitive fashion. The frequently observed fact that the lid closure coincided with stimulus onset may be evidence of some form of conditioning, the conditioned stimulus being the time interval between light flashes. If this is so and if, as has been argued elsewhere, introverts condition more easily than extraverts (Eysenck, 1957), this conditioned reaction would be likely to cut down the amount of light stimulation received by introverts as compared with extraverts, thus confounding the prediction. This may be overcome in future research by spacing the light stimuli at irregular intervals.

5. SUMMARY AND CONCLUSIONS

The effects of d-amphetamine sulphate, sodium amylobarbitone and meprobamate were compared with those of a placebo in respect of their power to influence subject's pupillary reactions to light stimulation. The main findings were: (i) that amylobarbitone retards responsiveness, while amphetamine increases it, and (ii) that drug conditions favouring rapid adaptation to the stimulus also appeared to produce greater sensitivity to the stimulus.

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DRUGS AND PERSONALITY

VIII. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS ON VISUAL AFTER-EFFECTS OF A ROTATING SPIRAL*

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1. INTRODUCTION

IN a previous paper in this series Eysenck, Holland and Trouton (1957) showed that the seen after-effects resulting from stimulation by means of a rotating spiral were increased very little by a stimulant drug and decreased significantly by a depressant drug. At that time there was little evidence that these after-effects were in fact correlated, as the theory demanded, with extraversion and introversion. Since then two separate experiments dealing with normal and neurotic subjects respectively produced very strong evidence in favour of this hypothesis (Eysenck, 1960), and it seemed desirable to repeat the experiment in order to discover whether the failure of the stimulant drug in the first experiment to produce very positive results was merely a chance effect or was in fact a genuine failure of the theory.

2. THE EXPERIMENT

Details of drugs, experimental design and subjects have been given in a previous paper (Eysenck and Easterbrook, 1960a). Eight subjects in all were tested under four drug conditions (d-amphetamine sulphate, sodium amylobarbitone, meprobamate, and a placebo), under an experimental design which ensured that each drug would be given once after each other drug and in each serial position. The experimental design, a balanced incomplete block, was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion here was only one of several applied to the same group of subjects under the same conditions.

The spiral, rotating at a speed of 100 r.p.m., was illuminated by twin spotlights in an otherwise dark room, and S was instructed to fix his vision on the silvered screw at its centre. After a short demonstration of the effect, S was instructed that the spiral would be started and stopped and that he should tell E when the after-effect had ceased. He was cautioned against mistaking the end of the spectacular immediate after-effect for the moment when the effect had completely disappeared. The measure was the time in seconds taken by stopwatch from the instant E turned off the spiral motor to the instant S announced

* We are indebted to the Wallace Laboratories for the support of the investigation.

† Now at the Burden Neurological Institute, Stapleton, Bristol.

the effect had ceased. A single reading was taken on each of four days after 45-second stimulation.

3. RESULTS

The mean durations of after-effect are shown in Table I. These results were relatively consistent as between replications, though the matrix failed to show a significant general effect of treatments. However, the greater duration of effect under the amphetamine as compared to the placebo treatment is significant by *t* test.

TABLE I

Mean Duration of After-Effect Following 45 Seconds' Stimulation with Spiral

		Treatments			
		Placebo	Amphetamine	Amytal	Meprobamate
Duration in seconds		24.05	29.64	23.11	24.97
Duration as percentage of individual totals (=100 per cent)		22.6	29.5	23.6	24.3

The duration of spiral after-effect may be an inverse measure of rate of recovery from visual stimulation. If so, it would be comparable with the rate of iris dilation after a continuing stimulus had been turned off. Measures of such rates were in fact available for these subjects (Eysenck and Easterbrook, 1960b), so that this possibility could be tested. When the differences between the treatment were expressed as percentages of the totals across treatments for both measures, as shown in Table I for the spiral after-effect durations, the agreement between these percentages was quite close. Analysis of variance was therefore conducted on a 6×4 matrix composed of two block means under each treatment for dilation rate (stimulus "off"), difference in dilation rate (stimulus "off"—stimulus "on") and the reciprocals of duration of spiral after-effect (each in percentage form). In this matrix, the effect of treatments was significant ($F=3.42$ with $3/20$ d.f.), the mean percentages being 28.1 for the placebo, 20.9 for amphetamine, 25.7 for amylobarbitone and 25.3 for meprobamate. The relatively slow recovery of amphetamine-treated subjects is the notable observation.

4. DISCUSSION

The results of the experiment are again in line with prediction, duration of the after-effects being longest for the stimulant drug (amphetamine) and shortest for the depressant drug (amylobarbitone). The effects of meprobamate, however, are not in the expected direction, and altogether the depressant drugs do not produce effects large enough to differentiate responses under them from placebo responses. The amphetamine conditions, however, do produce large and significant differences, so that the experiment may be said to be successful in clarifying the point which it was carried out to prove. It is difficult to know why the two experiments, although broadly giving similar results, differ in showing greater differences for depressant drugs in one case and for stimulant drugs in the other. It is possible that slight differences in experimental procedure may be responsible for this. Thus in the first experiment four readings were taken to make up each score, whereas in the present experiment only one reading was taken. This repetition would, according to our theory, favour the

accumulation of inhibition and might thus facilitate also the effectiveness of depressant drugs which are supposed to increase inhibition. Too little is known of the interaction of drugs and conditions to make it possible to advance this as anything but an *ad hoc* hypothesis, but as work in psychopharmacology becomes more accurate and begins to test specific hypotheses it will inevitably have to take into account and test such interactions. It is not impossible that we have encountered here one of the reasons for the frequent failures in this field to duplicate results when conditions are not precisely equated. An alternative possibility, of course, is that we are only dealing with chance differences here, and if larger numbers had been used no such differences between the two experiments would have occurred. Only further research will enable us to decide upon the accurate answer to this problem.

5. SUMMARY

The effects were studied of one stimulant and two depressant drugs on the seen after-effect of a rotating spiral, and compared with those of a placebo. As predicted the stimulant drug was found to have a facilitating effect, i.e. it prolonged the period of apparent movement after stimulation. The depressant drugs only differed slightly from the placebo in their effects, and did not, as in a previous experiment, give consistent and significant results. A theoretical explanation has been advanced to account for the differences in outcome between this and the previous experiment.

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DRUGS AND PERSONALITY

IX. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS UPON VISUAL FIGURAL AFTER-EFFECTS*

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1. INTRODUCTION

FIGURAL after-effects are the observable results of a hypothetical process of satiation or inhibition which accompanies and follows the passage of neural currents consequent upon stimulation. Most of the work in this field has been on figural after-effects affecting contours. In this work an inspection figure is fixated for a fairly lengthy period of time; this is then withdrawn and two test figures are substituted. One of these test figures falls within the same area as the inspection figure while the other is well removed from this area. Differences in size between the two figures which are objectively equal are usually observed and are supposed to be a consequence of satiation set up by the inspection figure (McEwen, 1958).

Other effects also may be observed and made the basis of measurement. Thus when a bright inspection figure is fixated for any length of time and is then withdrawn, then a test figure exhibited in the same region should look rather darker, as a consequence of satiation, than an equally bright test figure exhibited elsewhere. In this experiment we have used both of these phenomena, i.e. size effects and brightness effects, for the measurement of satiation.

Satiation phenomena have been brought into connection with personality in terms of a general hypothesis identifying satiation with the more general concept of reactive inhibition (Eysenck, 1957); it follows from this identification that extraverts under conditions of equal stimulation should show greater figural after-effects than introverts. This hypothesis has proved difficult to test because of difficulties encountered in ensuring equal stimulation. Experiments of this kind require visual fixation for several minutes, and the structures involved in maintaining fixation are also subject to inhibition. As this inhibition is again supposed to be greater in extraverts, these would tend to be poorer at fixating than introverts and would consequently receive less stimulation during equal periods of time, thus leading to the prediction that because of the lower degree of stimulation thus received, extraverts would show weaker figural after-effects. It is also possible that extraverts would receive less stimulation because satiation would soon block the perceptual pathways, thus reducing the amount of stimulation received by them as compared with introverts.

* We are indebted to the Wallace Laboratories for the support of the investigation.

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Fortunately these contradictory predictions can be reconciled by realizing that the satiation which gives rise to figural after-effects sets in rather quickly, possibly within a matter of milliseconds, while reactive inhibition sets in rather slowly, possibly in a matter of minutes. The prediction would seem to follow that when inspection periods are short, extraverts would show greater figural after-effects. When inspection periods are long, introverts would be expected to show greater figural after-effects. With intermediate periods no great difference would be expected (short in this connection means 30 seconds or less; long means 3 to 4 minutes). The evidence on these predictions has been reviewed elsewhere (Eysenck, 1960) and appears to support the hypothesis. Unfortunately different types of subjects and different experimental regimes were used in the different studies so that it is impossible to be certain at the moment whether or not the data do in fact prove the hypothesis.

Similar considerations affect the predictions which may be made about drug effects in relation to satiation. Depressant drugs would be expected to increase the size of figural after-effects, while stimulant drugs would be expected to decrease them. Again we would expect complications to arise from the fact that fixation too would presumably be affected by the drugs in a compensatory manner, and further complications may arise from the fact demonstrated in a previous paper that iris size is also affected by the drug, thus changing the amount of light admitted by the eye (Eysenck and Easterbrook, 1960). In these circumstances no very confident prediction can be made but clearly an exploration of the field may serve to set the stage for further experiments.

2. THE EXPERIMENT

Details of drugs, experimental design and subjects have been given in a previous paper (Eysenck and Easterbrook, 1960). Eight subjects in all were tested under four drug conditions (d-amphetamine sulphate, sodium amylobarbitone, meprobamate, and a placebo), under an experimental design which ensured that each drug would be given once after each other drug and in each serial position. The experimental design, a balanced incomplete block, was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion here was only one of several applied to the same group of subjects under the same conditions.

(a) *Brightness matching* was carried out in a manner designed to evoke satiation effects (Eysenck and Holland, 1958). The subject sat with his head on a chin-rest seven feet from a screen that had a faint red light in its centre. On to this screen were projected two semi-circles of light, which made a smooth junction vertically through the middle of the red light. The brightness of the right-hand light was variable by either the subject or the experimenter, that of the left-hand or standard light by E alone. In a dark room, after he had been dark-adapted* and instructed, the subject was required to make two matchings of the standard (1.5 lumens) patch while fixing the red light with the right eye, the other being masked by a shield on the head-rest, and then to make two more with the left eye. In each case the luminance of the variable patch was alternately set too high or too low by approximately one lumen, and the accuracy of match was read off a galvanometer. The subject was then instructed to close his eyes while E blocked off the variable semi-circle and raised the luminance of the standard to 2.5 lumens. S then stared at the fixation point for one and a

* Using the Admiralty RL Adaptometer MKIA with the indicator set at 1 and an aperture of 15.

half minutes with one eye, then, after appropriate readjustments, made two further matches with the alternate eye. This additional stimulation was presented once to each eye. The readings taken were the differences, expressed in galvanometer readings, between the intensity of the two lights. (For a more detailed description of the apparatus and methodology, and the underlying theories, see Eysenck and Holland, 1958.)

(b) *Size matching* was carried out according to the same programme as brightness matching, and with the subject seated in the same position. The apparatus consisted of two cathode ray tubes, one above the other, facing the same way as the subject and visible to him in a mirror, at a net distance of 18 feet. On each tube was projected a circle of variable diameter, subject to control in the manner described above. A red light was situated midway between the two tubes. The standard stimulus was set at a diameter of 6 cm. for matchings and at a diameter of 7 cm. during the satiation period, which lasted for two minutes on each occasion. In this case too the "experimental" measures were taken with the alternate eye so that retinal effects were excluded and would not be registered as evidence of satiation. The readings recorded were differences expressed in galvanometer readings between the sizes of the two circles. (For a more detailed description of the apparatus and methodology, and the underlying theories, see Eysenck, 1960.)

3. RESULTS

In the brightness matching test, on the assumption that satiation of the projection areas tends to reduce phenomenal brightness, the additional exposure of the standard stimulus at increased intensity was expected to cause the subject to set the intensity of the variable stimulus lower to match a phenomenally duller standard. In the circles matching test, additional stimulation with an over-sized standard was expected to cause a phenomenal displacement of the standard which would be reflected in smaller subsequent settings of the variable stimulus. These expectations were not borne out by the results which are shown in Table I, nor was there any relation between changes in variable stimulus setting and treatment, except for a tendency for the variable circle to be set larger in the descending matches under amytal treatment ($F=21.2$ with $3/3$ d.f.).

TABLE I

Brightness Matching Scores: 4 Pre-stimulation Trials Minus 4 Post-stimulation Trials in Arbitrary Units Excess of Standard Over Variable Illumination

			Placebo	Amphetamine	Amytal	Mepro- bamate
Block 1	..	..	9.5	10	1	2
Block 2	..	..	6.75	.25	3	21.25
Sum block	..	..	8.12	5.12	2	11.62

Size Matching Scores: 4 Pre-stimulation Trials Minus 4 Post-stimulation Trials in Arbitrary Units Excess of Standard Over Variable Size

			Placebo	Amphetamine	Amytal	Mepro- bamate
Block 1	..	..	-8	4.75	5.25	-7.50
Block 2	..	..	-4.5	5.5	-2.75	-15.25
Sum block	..	..	-6.25	5.12	1.25	-11.38

Results of analysis of variance: N.S.

Satiation dissipates with time. The first matches made after experimental stimulation ought therefore to be more likely to show the expected changes than later matches. The points of subjective equality (PSEs) and the intervals of uncertainty* for the control and first experimental settings on the brightness matching and size matching tests under the four treatments are shown in Table II. The data are presented as arbitrary dial readings representing excess of variable stimulus brightness or size over standard stimulus settings. Four points are evident in this table. First, errors in control settings vary with treatment in a consistent manner as between tests. Second, the differences of control settings made under the amylobarbitone treatment from those made under other treatments are similar to the differences of experimental from control settings for the other treatments (amytal is associated with similar errors to those arising from experimental stimulation). Third, the difference between control and experimental settings is markedly divergent under amytal from what it is under other treatments. Finally, in the size matching test under all treatments except amytal the difference in PSE between experimental and control treatments tends to take the predicted direction, but under amytal (and in all treatments on the brightness matching test) the difference has the opposite sign to that predicted.

TABLE II

Visual Matching Test Results in Units Excess of Variable Over Standard Settings
Treatments

	Placebo		Amphetamine		Amytal		Meprobamate	
	PSE	IU*	PSE	IU	PSE	IU	PSE	IU
<i>Brightness Matching:</i>								
Control ..	-8.81	8 $\frac{3}{8}$	-9.94	6 $\frac{1}{4}$	-6.75	6 $\frac{1}{4}$	-10.87	10 $\frac{7}{8}$
Experimental ..	-4.19	17 $\frac{3}{8}$	-6.38	11 $\frac{3}{4}$	-6.75	6 $\frac{1}{4}$	-8.37	6 $\frac{1}{2}$
Difference E-C ..	4.62		3.56		0.00		2.50	
<i>Size Matching:</i>								
Control ..	6.56	15	6.69	9 $\frac{7}{8}$	3.00	10	8.12	16 $\frac{3}{4}$
Experimental ..	4.69	13 $\frac{3}{8}$	4.87	10 $\frac{1}{2}$	4.87	13 $\frac{1}{4}$	7.87	10 $\frac{3}{4}$
Difference E-C ..	-1.87		-1.82		1.87		-0.25	

* Interval of Uncertainty. The difference between the average setting in the ascending order of adjustment and the average setting in the descending order.

It may be supposed that the effect of stimuli on performance in visual matching tasks would be related to the amount of light admitted to the retina—i.e. to iris size. That this is a tenable interpretation of the variations in control settings in the visual matching task is shown by the calculations displayed in Table III. There are shown, for the four treatments, the errors in control settings as percentages of the sum across treatments, together with iris sizes similarly expressed as percentages. The iris sizes have been treated (by subtraction of a constant 80 per cent. of the standard size from the means in Table 2 in the paper dealing with effects of drugs on the pupil—Eysenck and Easterbrook, 1960) to emphasize the variance between treatments. The agreement of these two sets of ratios suggests that the experimental stimulation was not equated as between treatments.

* The differences between the thresholds determined in the ascending and descending orders.

TABLE III
Relation of Visual Matching Errors to Iris Diameters

					Treatments			
					Placebo	Amphetamine	Amytal	Meprobamate
<i>Control settings as ratios of totals across treatments:</i>								
Brightness matching	..	..	..	..	24.2	27.3	18.6	29.9
Size matching	..	..	..	..	27.2	26.9	15.0	31.0
Mean	..	..	..	..	25.7	27.1	16.8	30.4
<i>Iris sizes (—k) as ratios of total across treatments</i>								
	..	..	..	..	26.0	28.5	16.0	28.5

The effect of the experimental stimulation on the errors of adjustment in the two visual matching tasks can be estimated in a way which compensates to some extent for the inequalities of stimulation. This is done by expressing the experimental settings under each treatment as ratios of the control settings under the same treatment. These calculations are displayed in Table IV, and they show that the reduction of initial error that occurs on the subsequent experimental settings is proportionately greatest with the placebo treatment,

TABLE IV
Visual Matching Test Results
Experimental Error per Unit Control Error as Ratios of Totals Across Treatments

					Treatments			
					Placebo	Amphetamine	Amytal	Meprobramate
Brightness matching	..	..	..	..	15.2	22.6	35.2	27.1
Size matching	..	..	..	..	18.9	19.8	35.6	25.6
Means	..	..	..	..	17.0	21.2	35.4	26.4

least with amylobarbitone. The effect of treatments is significant overall ($F=44.2$ with $3/4$ d.f.) but the differences between amphetamine treatment and either the placebo or meprobramate treatments are not. This, of course, is not a predicted relationship; amytal affects the difference in setting between control and experimental conditions but in the direction opposite to the prediction.

4. DISCUSSION

It cannot be said that the results bear out the expectation that depressant drugs would increase figural after-effects; while stimulant drugs decrease them. This may in part be due to the fact that the inspection time chosen (90 seconds in one case, 120 seconds in the other) was badly chosen from the point of view of the theory under investigation; much shorter periods would have been more appropriate. This was not realized when the experiment was designed and makes the results equivocal at best.

Another difficulty which arises in work of this kind and which may give rise to apparent contradiction, relates to the practice of using ascending and descending orders of presentation.

One of the earliest interpretations of figural after-effects to which Kohler's

satiation theory was opposed was that of "adaptation to the norm" (Gibson, 1933). Although applied originally in the context of perception of curved lines, this type of argument can be extended to many other perceptual tasks. Helson and co-workers (Helson, 1948; Michels and Helson, 1949, 1954) have elaborated an "adaptation level theory" which is said to predict changes in absolute and comparative judgments as a result of differences in the order of presentation of different stimulus values. Accordingly the experiments reported above were designed in such a manner that any after-effects demonstrated would be virtually independent of the order in which extremes on the continuum of variable (or comparison) stimuli were experienced.

The desired control against order effects was imposed by alternating directions of approach to the PSE on the comparison scale. This procedure may be said to have two sorts of effect: (a) it confounds order effects more or less effectively, and (b) it confounds the effects of "self-satiation" with the comparison stimulus (as Kohler and Wallach have described satiation due to experience with the test figure). On the other hand the distinction reflected in this statement may be invalid. Order effects and self-satiation effects may be identical. In fact satiation may be the mechanism of the adaptation which Gibson's (1933), Helson's (1948) or Johnson's (1949) theories describe—as Walker has suggested may be the case with the mechanism of the comparable reactive inhibition and that of increments to habit strength (1956).

In rationale the procedure used consists in stimulating an "experimental" cortical area in such a way as hypothetically to produce for instance an enhancement of the value of another stimulus subsequently presented to the same area. This change is then checked by approaching PSE with a similar but graduated stimulus projected on to another cortical area, *alternately from the end of the comparison scale which induces the same, and the end which induces the opposite, overt effects of satiation as those expected from the experimental stimulation*. It can be seen that success in demonstrating figural after-effects by this method is dependent on (a) inducing effects that will retain demonstrable magnitude until the comparative measures have been made, and (b) a perfection in counterbalancing of order effects which it is impossible to check by known means.

In view of the speed of dissipation of figural after-effects (e.g. Hammer, 1949), it is considered desirable to arrange the order of experience with the comparison figure deliberately so that self-satiation (or order effects) would operate to produce the same sorts of change in performance as those produced by satiation with the inspection figure. Thus in the test for Kinaesthetic Figural After-effect, the PSE on the comparison figure should be approached from the thin end if a wide inspection figure has been used with the expectation of inducing a shift of PSE towards the thin end of the wedge. The effect of self-satiation in the control area and the effect of satiation in the experimental area should then operate to produce the same sorts of change in judgment. Opposed to the apparent advantage of this method in rendering the phenomenon easier to investigate, is the dubious fault that it leaves open the possibility that the effects produced could be attributed to other causes. This fault is "dubious" because the "alternative" theories seem to operate at different levels of analysis, so that they are not competitors of the more fundamental satiation theory.

It is interesting to note that the results throw some light on perceptual errors quite independent of satiation and figural after-effects. Errors in control settings can be seen to follow with treatment for both the experiments; they are smallest for amylobarbitone, largest for meprobamate, with placebo and

amphetamine being quite small. It is difficult to account for this in view of the fact that both amylobarbitone and meprobamate are depressant drugs and might therefore be expected to react in the same direction. Here again is a finding where further research will be required before any definitive conclusions can be drawn.

5. SUMMARY

The effects of d-amphetamine sulphate, sodium amylobarbitone, meprobamate and a placebo were investigated with respect to two measures of figural after-effect. The results do not support the hypothesis that depressant drugs would increase figural after-effects, and that stimulant drugs would decrease figural after-effects. It was found that the main effects of the drugs were on errors in control settings, rather than on figural after-effects; these errors were increased most by meprobamate, least by amylobarbitone. Several hypotheses are suggested as to the reasons for the failure of the experiment to support the hypothesis.

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DRUGS AND PERSONALITY

X. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS UPON KINAESTHETIC FIGURAL AFTER-EFFECTS*

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1. INTRODUCTION

IN the previous paper we have given a brief discussion of the reasons why figural after-effects are of interest in the study of personality and why stimulant and depressant drugs would be expected to have certain effects upon them (Eysenck and Easterbrook, 1960a). In this paper we describe an experiment using kinaesthetic figural after-effects rather than visual ones. By and large results with kinaesthetic figural after-effects have been more clear-cut and definite in relating these after-effects to personality; several studies have shown extraverts to have greater figural after-effects than introverts (Eysenck, 1957). Furthermore there is at least one study demonstrating that stimulant and depressant drugs have the predicted results upon kinaesthetic figural after-effects (Poser, 1958). The reasons for this may be that whereas for visual experiments it is difficult to check on the subject's ability to maintain fixation, nothing comparable is required in experiments on kinaesthetic figural after-effects. Furthermore any departure from instruction on the part of the subject can easily be checked by the experimenter. For these reasons kinaesthetic tests have very definite advantages over visual ones.

2. THE EXPERIMENT

Details of drugs, experimental design and subjects have been given in a previous paper (Eysenck and Easterbrook, 1960b). Eight subjects in all were tested under four drug conditions (d-amphetamine sulphate, sodium amylobarbitone, meprobamate, and a placebo), in an experimental design which ensured that each drug would be given once after each other drug and in each serial position. The experimental design, a balanced incomplete block, was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion here was only one of several applied to the same group of subjects under the same conditions.

The apparatus for this test of kinaesthetic figural after-effect has been previously described (Eysenck, 1957). It consists of a graduated wedge along which the subject must find a width corresponding to the width of a standard

* We are indebted to the Wallace Laboratories for the support of the investigation.

† Now at the Burden Neurological Institute, Stapleton, Bristol.

block presented to his alternate hand. A stimulus block, narrower than the standard, is to be stroked to provoke "satiation". Four sets of control and post-satiation readings were taken, one in each of the four different orientations of the wedge, NE, SW, E and W in a constant order. Each set of readings consisted of four control measures and four experimental measures, the point of subjective equality being approached alternately from either end of the wedge in each case. The experimental measures were taken immediately after the subject had rubbed the stimulus block for thirty seconds with the hand he used to feel the width of the standard block. The subject was blind-folded throughout. The readings were points on an arbitrary scale attached to the wedge. The subjects were allowed to take their own time for each judgment, but the post-stimulation matchings were usually completed within a minute after the rubbing had been completed, the first of them being recorded within 10-15 seconds of that time.

3. RESULTS

The predicted effect of 30 seconds rubbing a smaller block in place of the standard was a displacement of the cerebral projection of the contours of the standard so as to make it seem relatively larger. This would be reflected in a larger setting of the variable stimulus. The results, both for the whole of the data and for the matrix composed only of the first post-stimulation readings, indicated greatest "satiation" under amytal treatment, least with the placebo or amphetamine. These results agree with prediction, but fail to reach acceptable levels of statistical significance.

The kinaesthetic matching test results are displayed in Table I. The means of the first post-stimulation readings and of all control readings indicate greatest error under amytal treatment and least error under placebo in both cases. In the lower half of the table are shown errors in control settings and error change scores, both expressed as percentages of the total across treatments. This form makes these results directly comparable with those previously reported for visual tests (Eysenck and Easterbrook, 1960a). In fact the agreement between the two sets of data is quite close.

TABLE I
Kinaesthetic Matching Test Results

				Treatments			
				Placebo	Amphe- tamine	Amytal	Mepro- bamate
					Units Excess of V over S		
<i>Differences E-C:</i>							
All data	..	..	0.03	-0.19	0.51	0.34	
1st readings only	..	..	-0.63	-0.05	1.11	-0.21	
<i>Mean Scores:</i>							
Control—all data	..	..	3.10	3.37	5.56	4.77	
Experimental (1st)	..	..	2.47	3.32	6.67	4.56	
Ratios of Treatment Means to Total Across Treatments							
Control errors	..	..	18.4	20.1	33.1	28.4	
Error change (E/C × 100)	..	..	20.7	24.7	30.5	24.1	

The differences between experimental and control measures in Table I correlate with both the control errors in the kinaesthetic test and with the calculations of experimental error per unit control error in the visual matching tests. These facts suggest that the indications of differential satiation in the kinaesthetic test and in the visual size matching test might possibly be regarded as reflecting consistent differences in capacity for correction of error. Indeed when the percentage scores from Table I are put into a matrix with the error change scores from Table IV of the preceding paper, the effect of treatments remains substantially unchanged and highly significant ($F=31.1$ with 3/12 d.f.). The mean percentages are: placebo, 18.3; amphetamine, 21.8; amytal, 33.6; and meprobamate, 26.3. The standard error of the difference between any two of these means is 1.66, so that only the differences between amphetamine and either the placebo or meprobamate treatments fail to reach significance. No such consistent result is found if the matrix be arranged so that high scores indicate satiation in the expected form. Of course the condition which prevents improvement in accuracy of matching may in fact be neural satiation.

4. DISCUSSION

The results of this experiment agree with prediction in showing that figural after-effects are greatest with amylobarbitone, least with amphetamine (all data) or placebo (first readings only). The results, therefore, agree with those of Poser but their failure to reach statistical significance makes it impossible to regard the prediction as finally proven.

It is again found that errors show drug effects more clearly than do calculations relating to figural after-effects. Results are very much in line with those in the paper on visual figural after-effects.

5. SUMMARY

The effects were tested of stimulant and depressant drugs on kinaesthetic figural after-effects. The hypothesis that stimulant drugs would decrease after-effects, while depressant drugs would increase them, was supported by the results, but only at a low level of statistical significance. It was found that liability to error in making settings under control conditions was affected much more strongly than were figural after-effects, and the results were very similar to those obtained previously with visual figural after-effects.

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DRUGS AND PERSONALITY

XI. THE EFFECTS OF STIMULANT AND DEPRESSANT DRUGS UPON AUDITORY FLUTTER FUSION*

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1. INTRODUCTION

SEVERAL workers have demonstrated a relationship between anxiety and critical flicker frequency (CFF); among these are Krugman (1947), Goldstone (1955) and Friedl (1954). Unfortunately the trait of *anxiety* is not unidimensional, being a compound of neuroticism and introversion, so that these data might indicate a lower threshold of CFF for neurotics, or for introverts, or for both. The second of these interpretations has been tentatively adopted (Eysenck, 1957), in spite of some questionnaire evidence to the effect that thresholds are lower for extraverts (Washburn *et al.*, 1930; Madlung, 1935; Simonson and Brozek, 1952). The main reason for not considering this additional evidence too convincing lies in the curious nature of the measures used to determine extraversion-introversion; these seem to compound introversion and neuroticism, as pointed out elsewhere (Eysenck, 1960). However, when we take into account the rather strong evidence regarding drug effects (Simonson and Brozek, 1952; Landis, 1954), which tends to show that stimulant drugs raise the threshold, while depressant drugs lower it, as well as the fact that brain injury tends to lower the threshold (Enzer *et al.*, 1944; Halstead, 1947; Landis, 1949; Werner and Thuma, 1942), then the case against this tentative hypothesis becomes rather strong. It may be that the attempt to relate CFF to only one dimension of personality was mistaken, and that CFF is related to both neuroticism and extraversion, in the sense that low thresholds characterize the more neurotic and the more extraverted person. This hypothesis would certainly account for all the available facts better than the original hypothesis.

A great deal of work has been done in this Department by Granger on drug effects on CFF thresholds (see also Holland's paper, which is number XII in this series), and the present study deals rather with auditory flutter, which has been suggested by several writers (Davis, 1955; Ogilvie, 1956) to be an auditory analogue of CFF. The hypothesis to be investigated is that *depressant drugs lower flutter fusion threshold, while stimulant drugs raise it*. There has become available some evidence that extraverts have lower thresholds than introverts (Eysenck, 1960), thus supporting our revised hypothesis, but the data are lacking in significance, and cannot be accepted as proving such a relationship.

* We are indebted to the Wallace Laboratories for the support of the investigation.

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2. THE EXPERIMENT

Details of drugs, experimental design and subjects have been given in a previous paper (Eysenck and Easterbrook, 1960). Eight subjects in all were tested under four drug conditions (d-amphetamine sulphate, sodium amylobarbitone, meprobamate and a placebo), under an experimental design which ensured that each drug would be given once after each other drug and in each serial position. The experimental design, a balanced incomplete block, was completed twice, once for the subjects seen in the morning and once for those seen in the afternoon. The test under discussion was only one of several applied to the same group of subjects.

The test used was the University of Chicago Sound Discrimination Test, which has been designed and developed in the Section of Medical Psychology under the direction of W. C. Halstead. Detailed information on the test may be obtained from the manual, but the following brief description may be useful. The test is administered by tape recorder. The signal consists of interrupted "white" noise with square wave characteristics at an intensity of 70 db. Repetition rates vary between 10 and 150 i.p.s., in steps of 10, and the sound-time fraction is 0.90. There are four random presentations of the fifteen frequencies by the method of constant stimuli. Instructions, examples, and practice items are all contained in the first part of the recording, and they are reported as being adequate for normal subjects of average intelligence. The test presents the subject with short bursts of white noise in pairs, and the subject is instructed to report whether the two sounds were the same or different. Three scores were taken from each record: the frequency of interruption at which the second judgment of "same" was made; the threshold in the same terms by standard methods, and the interval of uncertainty, defined as the range in c.p.s. between the points at which 25 per cent. and 75 per cent. of the pairs were judged "same".

3. RESULTS

Table I shows the mean results from this test. Although the two threshold estimates are consistent with one another in showing improved discrimination under all drugs, this result is devoid of statistical significance, and cannot even be regarded as suggestive ($F = .06$ and $.02$). The interval of uncertainty, which is the difference in c.p.s. between the flutter frequency and the fusion frequency (each measured at the relevant quartile) is a slightly more reliable measure, and gives higher values, showing greater uncertainty, for all drug conditions. The F ratio for treatments, using the variance between replications as an estimate of error, is again insignificant ($F = 2.4$, with 3/13 degrees of freedom).

TABLE I
Auditory Flutter Fusion Test Results

	Treatments			
	Placebo	Amphetamine	Amytal	Meprobamate
Fusion frequency in c.p.s.:				
(a) Second "same"	50.0	53.75	51.25	53.75
(b) Point of subjective equality	75.18	77.87	76.06	77.06
Interval of uncertainty	52.75	67.00	63.96	62.07

4. DISCUSSION

In view of the regularity with which drug effects have been found in relation to CFF thresholds, it is a little surprising to note the complete failure of the

present experiment. It is possible that flutter fusion is more unreliable as a test, particularly when measurement is not carried out in a sound-proof room. Alternatively, it is possible that flutter fusion is not a true analogue physiologically of flicker fusion; in particular the lateral inhibition so characteristic of CFF phenomena may not be at all apparent in the present test. In view of the strong opinion of experts that the two phenomena are similar it might be wise to await duplication of the present findings before coming to any definite decision.

5. SUMMARY

The effects of d-amphetamine sulphate, sodium amylobarbitone and meprobamate were compared with those of a placebo in respect to their power to affect the threshold of auditory flutter fusion. No significant effects were observed.

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DRUGS AND PERSONALITY

XII. A COMPARISON OF SEVERAL DRUGS BY THE FLICKER-FUSION METHOD

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1. INTRODUCTION

THE phenomenon of flicker fusion requires no elaboration to the modern reader. Its psychological, physiological, physical determinants have been outlined by an immense literature (1). Even the limited field of the effects of chemical agents on flicker and fusion is great. In a recent review Landis (2) went so far as to suggest that CFF might be employed as a method of standardizing the depressant effects of somnifacient drugs (Landis (2)). Despite contradictions, which may occur due to the biphasic characters of certain drug effects, the barbiturates and similar depressant compounds tend to depress CFF whereas the stimulants tend to raise it. The effects of alcohol and caffeine are still unclear (Simonson and Brozeck (3)). Whether the drugs affect the organism towards greater or lesser total sensitivity or whether the changes are due to some complex function of, say, the light/dark ratio is also unclear.

The present report is one of a drug study in which flicker changes have been used, rather than investigated. For this reason the conditions have been held constant from day to day and the changes assumed to represent the action of the agent taken. It would, perhaps, be more accurate to designate the experimental conditions as a "flickering situation". Data are available from two studies. The first of these has been reported elsewhere (Eysenck, 1960) (4), and will be combined with the second (the present) because of their relevance to each other. The physical conditions and the experimental method are identical for both investigations.

2. SUBJECTS AND APPARATUS

The first group consisted of 24 subjects who were tested on each of three consecutive days. They received three treatments: (a) meprobamate (2-methyl-2-n-propyl-1, propanediol dicarbamate) 400 mg., (b) doriden (glutethimide-3-phenyl-3-ethyl-2, 6-dioxopiperidine), 250 mg. and (c) no drug, in a balanced design. The second study was smaller and 6 subjects were again tested on three occasions, with a one-day interval between each session, this time receiving: (a) sodium amylobarbitone 3 grains, (b) d-amphetamine sulphate 10 mg., and (c) placebo. The experimental design ensured randomization of treatments. Both drugs and the placebo were administered in identically appearing capsules. The groups were tested approximately $1\frac{1}{2}$ hours after administration of the drugs.

The first group comprised both sexes with a mean age of 30 S.D., 8 years. The second group was female with a mean age of 20.33 and a range between 19-24 years.

The instrument used to investigate peripheral flicker thresholds was a modified Lister moving arm perimeter (Type 315/466). The perimeter has its own illumination source and was modified to carry, instead of fixed targets, a small neon bulb (Type CV 988) which at its highest point was 290 mm. away from the eye and subtended an angle of 1.8° . The neon was activated by a pulse generator and a make and break finger key placed between generator and bulb.

After adequate demonstration and practice, ascending and descending thresholds were determined at 14 positions in the left temporal visual field: along the horizontal and 135° meridian at 10, 30, 45, 60, 70, and 80 degrees, and along the 45° meridian at 10, 25, 50 and 60° positions. The method of limits was employed, and the successive "bursts" of light were about three seconds in length with a three-second interval between. Both periods were assessed subjectively and are, therefore, approximate. During the "off" periods the frequency was changed in one cycle steps. The right eye was occluded throughout testing by a black surgical patch.

3. RESULTS

Results are presented here for the present investigation but both studies are summarized in Tables IV and V.

In the present study, analyses of variance have been conducted on the mean scores for the three individual meridians. These are outlined in Tables I, II, and III.

TABLE I
Outline of Analysis of Variance
(Left temporal field 45° meridian)

Source				d.f.	S.S.	M.S.V.	F	P
People	..	..	..	5	781.33	156.27	4.39 >	5%
Drugs	..	..	..	2	517.33	258.67	7.27 >	1%
Orders	..	..	..	2	37.33	18.67	—	—
Residual	..	..	..	8	284.51	35.56		
Total				17	1,620.50			
t A.B. = 3.791 > 1%				A — Amytal				
t A.C. = 2.792 > 5%				B = Dexedrine				
t B.C. = .99 —				C = Placebo				

TABLE II
Outline of Analysis of Variance
(Left temporal field 90° meridian)

Source				d.f.	S.S.	M.S.V.	F	P
People	..	..	..	5	415.70	83.14	2.268	N.S.
Drugs	..	..	..	2	284.10	142.05	3.876	5%
Orders	..	..	..	2	73.00	36.50	—	—
Residual	..	..	..	8	293.20	36.65		
Total				17	1,066.00			
t A.B. = 2.696 5%				A = Amytal				
t A.C. = 1.958 N.S.				B = Dexedrine				
t B.C. = — —				C = Placebo				

TABLE III
Outline of Analysis of Variance
(Left temporal field 135° meridian)

Source	d.f.	S.S.	M.S.V.	F	P
People	5	641.45	128.29	1.49	N.S.
Drugs	2	327.58	163.79	2.48	N.S.
Orders	2	32.25	16.33	—	—
Residual	8	527.84	65.98		
Total	17	1,529.12			

They indicate that with such a small sample as six subjects the drug variance is significant in two out of the three cases. In the third case it just falls short of the 5 per cent. level of confidence.

As the physical conditions of the experiment are identical with the one previously mentioned comparisons are available for six treatment conditions. These are presented in Tables IV and V.

TABLE IV

Flicker Scores for the Three Meridians Examined. Values are Representative of the Six, Four, and Four Positions Measured

	Horizontal Meridian	45° Meridian	135° Meridian	Total
1. Doriden (250 mg.) ..	33.48	28.96	32.02	94.46
2. Meprobamate (400 mg.) ..	35.18	30.78	33.98	99.94
3. Amytal (195 mg.) ..	36.26	31.16	34.58	102.00
4. No drug	35.58	32.86	35.44	103.88
5. Placebo	38.30	35.84	37.76	111.90
6. Dexedrine (10 mg.) ..	39.16	37.50	38.50	115.16
Means	36.326	32.850	35.380	104.557

TABLE V

Table of Threshold Scores at Different Positions in the Left Temporal Field for the Several Drugs Used

		Horizontal Meridian					
		10	30	45	60	70	80
1. Doriden	40.92	36.62	34.20	31.38	30.38	27.38	
2. Meprobamate	41.94	38.66	35.88	33.80	31.88	28.92	
3. Amytal	42.51	39.66	36.00	34.66	33.50	30.16	
4. No drug	42.44	39.10	36.32	34.02	32.24	29.62	
5. Placebo	44.94	42.34	40.16	36.66	34.16	31.66	
6. Dexedrine	45.00	43.66	40.00	37.32	36.32	32.66	
		135° Meridian					
		10	30	45	60	70	80
1. Doriden	37.80	32.46	29.62	28.16			
2. Meprobamate	38.30	35.46	32.20	29.96			
3. Amytal	38.66	36.00	32.50	31.16	30.00	28.82	
4. No drug	40.12	36.80	33.96	30.88			
5. Placebo	41.50	38.00	37.00	34.16	31.16	30.16	
6. Dexedrine	41.16	39.50	37.66	35.66	33.16	30.82	
		45° Meridian					
		10	25	50	60		
1. Doriden	36.38	31.04	25.38	23.08			
2. Meprobamate	37.54	33.00	28.04	24.54			
3. Amytal	37.34	32.66	28.34	26.34			
4. No drug	39.08	34.40	29.76	27.80			
5. Placebo	39.34	37.50	33.34	33.16			
6. Dexedrine	40.66	40.50	36.16	32.66			

4. DISCUSSION

An examination of these tables reveals several interesting features. The first of these is that the accepted depressant drugs—the hypnotic doriden, the tranquillizer meprobamate, and the barbiturate sodium amytal—have the three lowest thresholds followed by the “no drug” and placebo conditions. The highest threshold is given by the stimulant d-amphetamine sulphate. From the obtained results it would also appear that 250 mg. of doriden and 400 mg. of meprobamate depress thresholds more than the barbiturate (3 grains). This is probably a dosage effect and to assess it adequately is required some kind of baseline or intensity level . . . not an impossible task.

The final feature of interest is the fact that the placebo has raised the threshold from the “no drug” level. It would appear that placebo, in this small group, is acting something like a mild stimulant. One reason why such pill-taking effects may appear similar to mild stimulation lies in the tendency observed in subjects, after taking a pill of any kind, to be a little more introspective and possibly introverted. On Eysenck's (5) theory of personality it might be expected that this increased alertness and attention (in its widest sense) would lead to the slight increase observed.

The test results have, on the whole, supported Landis' belief that the flicker-fusion method, which is highly reliable with little diurnal variation, might be used as a standardization procedure for the operational definition of drug effects. Even in its less rigorous application, epitomized by this report, the flicker method may permit useful comparisons.

5. SUMMARY

An experiment is reported in which the effects of depressant and stimulant drugs are studied on critical flicker fusion frequency. Thresholds are lowered by the three depressant drugs used—doriden, meprobamate, and sodium amytal, and raised by the stimulant drugs—dextedrine. The placebo was also found to raise the threshold level above that of the “no drug” condition.

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PHENYLKETONURIA

A REVIEW AND A REPORT OF THE PATHOLOGICAL FINDINGS IN FOUR CASES

By

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PHENYLKETONURIA is an inborn error of metabolism characterized by excretion of phenylpyruvic acid in the urine and usually by severe mental defect and certain bodily features of which dilution of pigment is the most noticeable.

Følling first described the disorder in 1934 and since then the primary metabolic abnormality has been identified as an inability to oxidize phenylalanine to tyrosine (Jervis, 1947) due to the liver enzyme, which normally catalyses this reaction, being inactive (Jervis, 1953; Wallace, Moldave and Meister, 1957; Mitoma, Auld and Udenfriend, 1957). Although a precise correlation between the clinical, biochemical and neuropathological aspects of the condition is not yet possible, we felt it worth while to review the present position in an attempt to define the gaps in knowledge which continue to hinder such a correlation.

PATHOGENESIS

Estimations of the incidence of phenylketonuria vary, but probably about 0.6 per cent. of the institutionalized defectives and 4 per 100,000 of the general population are phenylketonuric (Jervis, 1937, 1954; Munro, 1947). However, the condition may be rare in certain races, and only isolated cases have been reported in Jews (Cohen and Kozinn, 1949) and Negroes (Ferreira-Fernandes, 1950).

Analysis of data in large series of patients has indicated that the condition is caused by the action of a single autosomal recessive gene (Jervis, 1938; Følling, Mohr and Ruud, 1944; Munro, 1947). Phenylketonuria occurs only in persons who are homozygous for this condition when the disorder invariably develops. The heterozygote is clinically normal and phenylpyruvic acid is not excreted in the urine. However, the presence of the single abnormal gene usually results in some defect of the enzyme activity, the heterozygotes showing a diminished capacity to metabolize large doses of phenylalanine. Thus, a phenylalanine tolerance test in these individuals tends to exhibit abnormally high and persistent blood levels of the amino-acid, presumably caused by a decreased phenylalanine hydroxylase activity (Hsia, Driscoll, Troll and Knox, 1956; Hsia, Paine and Driscoll, 1957; Hsia, 1958).

The primary abnormality in phenylketonuria is an inability to hydroxylate phenylalanine to tyrosine. Normally there are three components involved in this enzyme system, a non-protein co-factor, a stable fraction widely dispersed

throughout the body and an unstable fraction found only in the liver. It is this latter fraction which is lacking in phenylketonuria (Wallace, Moldave and Meister, 1957; Mitoma, Auld and Udenfriend, 1957; Kaufman, 1958).

As a result of this primary defect abnormalities occur which may be immediate or remote. As an immediate consequence of the block in hydroxylation, the concentration of phenylalanine in the blood plasma rises from normal levels of about 0.5–1.5 mg./100 ml. to values ranging from 20–60 mg./100 ml. and a similar rise occurs also in the C.S.F. (Jervis, Block, Bolling and Kanze, 1940; Borek, Brecher, Jervis and Waelsch, 1950; Knox and Hsia, 1957). Phenylalanine appears also in the urine together with phenylpyruvic acid, phenyllactic acid and the conjugate of phenylacetic acid, phenylacetylglutamine. Typical urinary excretion values for these substances are, in mg./100 ml.: phenylalanine 38, phenylpyruvic acid 50, phenyllactic acid 51 and phenylacetylglutamine 53 (Woolf, 1951). p-Hydroxyphenyllactic acid and p-hydroxyphenylacetic acid (Boscott and Bickel, 1953) are probably formed from the parent compound by non-specific hydroxylation (Dalglish, 1954). o-Hydroxyphenylacetic acid is also found in the urine (Armstrong, Shaw and Robinson, 1955; Boscott and Kirman, 1955). It is thought that the block of the normal hydroxylation in the para position allows the subsidiary process of o-hydroxylation to occur (Armstrong and Shaw, 1955), though it has been suggested that phenylpyruvic acid is the precursor (Tashian, 1959).

However, it is doubtful whether any of these substances are the immediate cause of the mental defect. Certainly there is no correlation between the concentrations of phenylalanine or its metabolites and the degree of mental deficiency (Borek, Brecher, Jervis and Waelsch, 1950; Jervis, 1950, 1952; Armstrong, Shaw and Robinson, 1955); the phenylalanine content of protein, as judged by its estimation in haemoglobin, is normal (Allen and Schroeder, 1957) and there is no good evidence that the abnormal metabolites of phenylalanine found in phenylketonuria are themselves toxic to the brain in the amounts occurring *in vivo*. One group of workers suggests that o-tyramine, which might be formed via o-tyrosine, could be toxic and cause mental defect (Mitoma, Posner, Bogdanski and Udenfriend, 1957). If this were so, a monoamine oxidase inhibitor, such as iproniazid, might be expected to cause a deterioration in phenylketonurics, by retarding the inactivation of o-tyramine. However, a 6-months controlled trial of iproniazid in 8 phenylketonurics, in which the drug was given to counteract the deficiency of adrenaline, noradrenaline or 5HT, revealed no evidence of deterioration either clinically, electroencephalographically or by intelligence testing (Kirman, Pare, Sandler and Stacey, 1959).

Secondly, there are the remote consequences of the block in phenylalanine metabolism. A theoretical deficiency of tyrosine will not account for the mental deficiency. The body does not rely on the formation of tyrosine from phenylalanine as tyrosine is a normal component of the diet. In fact the blood levels of tyrosine are fairly normal, as judged by the results of the phenylalanine-tyrosine ratio when compared with the simple phenylalanine tolerance test (Hsia, Driscoll, Troll and Knox, 1956; Hsia, Paine and Driscoll, 1957; Hsia, 1958). However, the excessive concentrations of phenylalanine in the blood may have an inhibitory effect on tyrosinase, the enzyme which metabolizes tyrosine, and so it is possible that there is a deficiency of substances along this pathway, stemming from such an inhibition (Fig. 1) (Dancis and Balis, 1955; Bickis, Kennedy and Quastel, 1957; Miyamoto and Fitzpatrick, 1957). Cowie (1951a) was the first to try the effect of feeding tyrosine and others have repeated

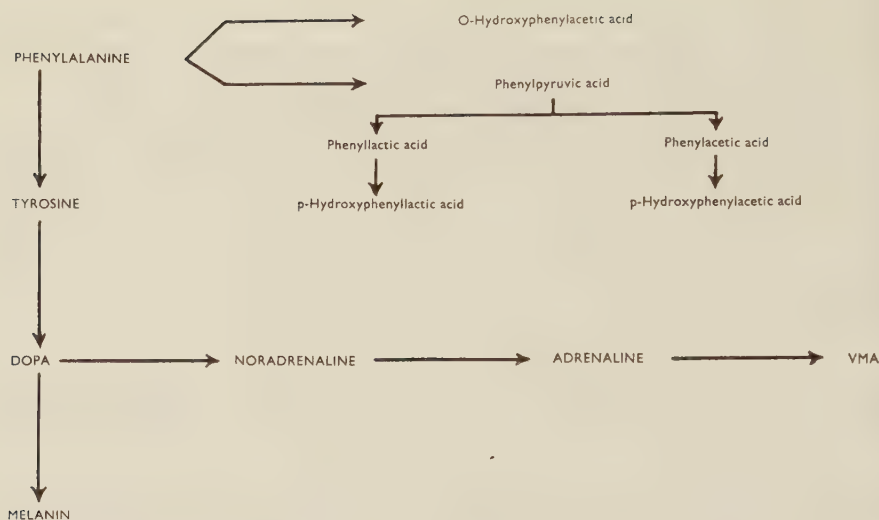


FIG. 1.—The normal pathway of phenylalanine metabolism and some of the abnormal metabolites of the amino-acid, found in the urine in phenylketonuria.

the experiment (Snyderman, Norton and Holt, 1955). The hair may become darker and so presumably the additional tyrosine increases melanin formation, but it has no effect on intelligence. The hair darkening which occurs with a phenylalanine-restricted diet may be due to lessening of the inhibition of tyrosinase consequent on the reduction of phenylalanine in the blood (see below).

It is likely that there is a deficiency of adrenaline and noradrenaline formation in phenylketonuria. Weil-Malherbe (1955) has demonstrated a deficiency of a substance with the biochemical characteristics of adrenaline in blood platelets from phenylketonurics; Cawte (1954, 1957) has found an abnormal sensitivity of the blood pressure response to injections of adrenaline and Armstrong (1958) a decreased output of 3-methoxy-4-hydroxy-mandelic acid (VMA), one of the main end-products of adrenaline and noradrenaline metabolism (Armstrong, McMillan and Shaw, 1957) in a small number of affected children he investigated. These abnormalities can again be traced back to the specific defect of phenylalanine hydroxylation, because the abnormal metabolites of phenylalanine have been shown, *in vitro*, to inhibit the enzyme responsible for decarboxylating 3,4-dihydroxy-phenylalanine (DOPA), (Fellman, 1956), which is the precursor of noradrenaline and adrenaline (Fig. 1). As catechol amines probably play an essential part in normal brain functioning, this may well be of importance in relation to the mental deficiency.

The demonstration by Armstrong and Robinson (1954) of indolelactic acid in the urine, suggested an abnormality of tryptophan metabolism in phenylketonuria. Following this lead, Pare, Sandler and Stacey (1957) showed that phenylketonurics had a deficiency of 5-hydroxytryptamine (5HT) in the blood and a similar deficiency of 5-hydroxyindoleacetic acid (5HIAA) which is the end product of 5HT metabolism, in the urine, when compared with normal controls and with mental defectives of the same age and in the same hospital. This finding has now been repeated in a larger series (Pare, Sandler and Stacey, 1959) and the low output of 5HIAA confirmed by independent workers (Berendes, Anderson, Ziegler and Ruttenberg, 1958; Baldrige,

Borofsky, Baird, Reichle and Bullock, 1959). Such a deficiency of 5-hydroxyindoles might be due to a defect in hydroxylation of tryptophan, similar to that of phenylalanine (Pare, Sandler and Stacey, 1957). However, an alternative explanation may rest in an inhibition of 5-hydroxytryptophan (5HTP) decarboxylase, the enzyme responsible for the production of 5HT from its precursor 5HTP (Fig. 2). Thus Davison and Sandler (1958) have shown that

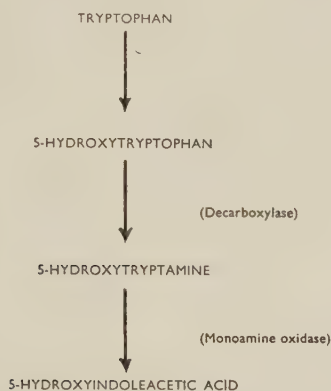


FIG. 2.—Illustrating the production of 5-hydroxytryptamine by the decarboxylation of 5-hydroxytryptophan, and its inactivation by monoamine oxidase and ultimate excretion in the urine as 5-hydroxyindoleacetic acid.

phenylpyruvic acid, phenylacetic acid and phenyllactic acid inhibit 5HTP decarboxylase *in vitro* and phenylacetic acid, at least, has a similar action *in vivo* (Davison, Ruthven and Sandler, 1959; Sandler and Close, 1959; Sandler, Davies and Rimington, 1959). Such a decreased 5HTP decarboxylase activity has been demonstrated in phenylketonuria by Pare, Sandler and Stacey (1958). They also showed that the 5-hydroxyindole deficiency could be corrected by reducing the concentrations of aromatic metabolites of phenylalanine by a phenylalanine-restricted diet (Pare, Sandler and Stacey, 1958; Baldrige, Borofsky, Baird, Reichle and Bullock, 1959). Since 5HT is thought to be of importance in normal brain functioning, this deficiency may also be a factor in relation to the mental defect. That it is not the only factor, however, is suggested both by the absence of a correlation between intelligence and 5-hydroxyindole values in blood or urine (Pare, Sandler and Stacey, 1959) and by the lack of any improvement in I.Q. following treatment designed to increase brain concentrations of 5HT (Kirman, Pare, Sandler and Stacey, 1958).

Finally there is the possibility that phenylalanine metabolites inhibit the formation of γ -aminobutyric acid (Hanson, 1958) which is again thought to be important in normal brain functioning (Elliott, 1959; Tower, 1959). Other biologically active amines, as yet little investigated, may also be involved.

To summarize, it seems likely that the mental defect in phenylketonuria is caused by the indirect action of aromatic metabolites of phenylalanine, acting on various enzyme systems and resulting in a deficiency of certain substances essential to normal brain functioning (Pare, Sandler and Stacey, 1959). Such inhibitory mechanisms acting on tyrosinase, DOPA decarboxylase, 5HTP decarboxylase and possibly glutamic acid decarboxylase, have been described.

CLINICAL

It is probable that the maternal liver protects the foetus adequately during intra-uterine life and that the phenylketonuric child is normal at birth. The plasma phenylalanine increases in concentration during the first few weeks of life but phenylpyruvic acid may not appear in the urine until after the fifth week (Armstrong and Binkley, 1956). Woolf and his associates conclude that the child is mentally normal at birth, deterioration ensuing rapidly over the first few weeks or months of life (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). The evidence for this view is necessarily tenuous, relying as it does on the assessment of the motor reactions of the new-born child and comparing it with the wider interests and abilities attained as the child gets older. However, further evidence as to the occurrence of intellectual deterioration and possibly irreversible brain damage, can be drawn from the results obtained with a phenylalanine-restricted diet when treatment is started in the first few months of life (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958) (see below). It is certain that after 2-3 years, most untreated phenylketonurics are of idiot level and remain at a nearly stationary mental age (Paine, 1957), while some authorities believe that further deterioration may continue over a long period.

There is a wide variation in attainment of normal childhood milestones but, on average, phenylketonurics will sit at 12-15 months and walk at 2½ years (Paine, 1957). About half the cases never learn to talk (Knox and Hsia, 1957). However, about one per cent. of cases have an I.Q. above 70 (Table I) and occasional cases have been reported with normal or near-normal intelligence (Cowie, 1951b; Cowie and Brandon, 1958; Low, Armstrong and Carlisle, 1956; Coates, Norman and Woolf, 1957; Hsia, Knox and Paine, 1957). Such cases have been reviewed by Hsia, Knox and Paine (1957), who have shown that the I.Q. cannot be accounted for by such possibilities as partial chemical blockage, mild variants of the gene or the patient being a heterozygote. Thus the reason for the wide variation in intelligence remains unexplained.

TABLE I
Distribution of I.Q. in 330 Phenylketonurics (Jervis, 1954)

I.Q.	Below 10	11-20	21-30	31-40	41-50	51-60	61-70	Above 70
Number ..	122	88	41	34	31	7	4	3
Per cent. ..	37	26	12	10	9	2	1	0.9

The general physical development is relatively unimpaired and phenylketonurics stand out among other children of comparable mental level by their lack of gross physical defects. However, a general dwarfing and a slightly reduced head circumference are not uncommon, especially in the most defective children, and epicanthic folds, widely spaced incisor teeth, pes planus and partial syndactyly of the toes may also occur (Jervis, 1937; Penrose, 1946; Cowie, 1951a; Paine, 1957). Phenylketonurics tend to have fairer hair than their normal siblings (Cowie and Penrose, 1951) and lighter coloured eyes (Berg and Stern, 1958). The skin is usually soft, smooth and fine in texture and between 20-30 per cent. patients show a tendency to dermatitis (Cowie, 1951a and b; Knox and Hsia, 1957; Paine, 1957). This may range from severe eczemoid lesions to mild eruptions, or only a dry, rough or scaly skin. The lesions occur especially on wet or exposed parts of the body and may be simply

the result of an increased sensitivity of the skin to the trauma habitually sustained by a defective child (Knox and Hsia, 1957). It is noteworthy that phenylketonurics tan in response to sun or ultraviolet lights and histochemical studies of excised irradiated skin have shown that the pigment activity of the melanocytes is normal (Hassel and Brunsting, 1959).

Neurological examination reveals no abnormality in phenylketonurics with higher levels of intelligence, but, as the mental defect becomes more pronounced, features suggestive of "extrapyramidal" abnormality become apparent. Jervis (1937) claims that about two-thirds of the most severely defective cases have neurological signs. These include a stooped posture, muscular hypertonicity with hyperactive reflexes, tremor of the outstretched hands or digital mannerisms such as flicking, twiddling or pill-rolling movements (Cowie, 1951a; Hilliard and Kirman, 1957; Paine, 1957), though these signs are quite unspecific. Spasticity or pyramidal signs are uncommon, though Cowie (1951a) reported 3 patients with extensor plantar responses. Epilepsy is a common feature in phenylketonuria, occurring in 25 per cent. of 418 patients in whom this symptom was looked for (Jervis, 1954). As with other neurological abnormalities, epilepsy is commoner in the more severely defective cases. Thus, in one series, 26 out of 78 (33 per cent.) patients with an I.Q. of less than 25 had a history of fits, compared with only 2 out of 28 (7 per cent.) patients with an I.Q. of over 25 (Paine, 1957). The seizures usually start before the age of 2 years and may cease spontaneously in later childhood. They are usually infrequent, but are often difficult to control by ordinary anticonvulsant drugs (Wright and Tarjan, 1957).

Electroencephalography reveals an abnormality in the majority of cases whether or not the patient has overt epilepsy. The commonest is a non-specific generalized epileptic activity (Gibbs and Gibbs, 1941; Pond, 1959), but hypersarrhythmia, spike and wave formation and non-specific low-voltage activity are not uncommon (Paine, 1957; Low, Bosma and Armstrong, 1957).

Cerebral arteriovenous oxygen studies suggest that cerebral metabolism is reduced in phenylketonurics (Himwich and Fazekas, 1940, 1944).

Diagnosis is made by adding a 5 per cent. solution of ferric chloride, preferably acidified, to urine. When phenylpyruvic acid is present, a characteristic olive-green coloration is produced which develops several seconds after the addition of the ferric chloride solution, quickly reaches a maximum intensity and fades in 15 minutes to half an hour. This reaction is positive in all phenylketonurics after about the fifth week in life unless on a reduced phenylalanine diet. The diagnosis can be confirmed by chromatographic examination of the urine.

TREATMENT

Obviously the most rational therapy is to reduce the concentrations of the phenylalanine metabolites which directly, or more probably indirectly, are thought to cause the mental defect. All dietary proteins are about equally rich in phenylalanine and a suitable diet can therefore be devised only by supplying the bulk of the nitrogen as a mixture of amino-acids, the cost of which would be prohibitive. However, protein hydrolysates can be freed from phenylalanine, tyrosine and tryptophan by passing through a column of charcoal. A casein acid hydrolysate, made phenylalanine-free in this way and with tyrosine and tryptophan, minerals and vitamins added, was suggested by Woolf as a suitable dietary treatment for phenylketonuria. Such a diet was first fed to a phenylketonuric by Bickel, Gerrard and Hickmans (1953) who reported marked

improvement in the child's mental condition. Since then numerous reports on the efficacy of this regime have appeared (Woolf, Griffiths and Moncrieff, 1954; Woolf, Griffiths and Moncrieff, 1955; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958; Armstrong and Tyler, 1955; Blainey and Gulliford, 1956; Horner and Streamer, 1956; Hsia, Knox, Quinn and Paine, 1958; Brimblecombe, Stoneman and Maliphant, 1959). The biochemical abnormalities characteristic of phenylketonuria disappear within a few weeks depending on the degree of phenylalanine restriction (Woolf, Griffiths and Moncrieff, 1955; Pare, Sandler and Stacey, 1958). The clinical signs likewise improve in the first few months. Skin lesions clear up and in most patients new-grown hair is darker (Armstrong and Tyler, 1955; Woolf, Griffiths and Moncrieff, 1955). Perhaps the most convincing evidence of improvement is the decrease in number or the complete cessation of epileptic fits and the disappearance of abnormal patterns in the electroencephalogram, relapse occurring as soon as the diet is withdrawn (Bickel, Gerrard and Hickmans, 1953; Armstrong and Tyler, 1955; Woolf, Griffiths and Moncrieff, 1955; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958; Horner and Streamer, 1956; Low, Bosma and Armstrong, 1957).

Taken as a whole the reports strongly suggest that the diet benefits the mental defect in phenylketonuria. In a child of idiot level, this benefit rarely amounts to more than an alleviation of a still severe mental defect and any improvement occurs slowly over a period of months or years, in contrast to the rapid disappearance of other signs. However, Woolf and his associates believe that, by starting the diet sufficiently early in life, severe mental deficiency can be prevented and a relatively high I.Q. maintained (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). These authors maintain that improvement can only be expected in children under the age of 2 years, though treatment is worth while up to the age of 4 years in brighter children with an I.Q. of 40 or over. They suggest that after a certain period, irreversible brain damage occurs. Taking into account the fact that only one per cent. of untreated phenylketonurics have an I.Q. over 70, their results in patients treated early in life are suggestive. These results, compared with those when treatment was started later, add substance to the suggestion of the development of irreversible brain damage.

If this is so, early treatment is essential. When phenylketonuria is suspected at birth, because of a family history, the urine should be tested at weekly intervals for the first two months of life, after which time, if the ferric chloride test is negative, the parents can be reassured that the child is not phenylketonuric. A simplified, yet reliable, test has recently been developed whereby a strip of reagent-impregnated paper, folded in a wet nappy, gives an immediate colour reaction if phenylpyruvic acid is present ("Phenistix", Ames, Co.). It has been suggested that these might be used to screen all babies at three weeks of age (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). However, since only about 4 per 100,000 babies are phenylketonuric, the expense in both time and money would be considerable. Certainly all babies who are slow to develop should be so tested.

The practical difficulties of treatment with a phenylalanine-restricted diet are substantial. For the treatment to succeed, the blood levels of phenylalanine must be kept within normal limits. Lack of phenylalanine results in the child failing to grow (Berry, Sutherland, Guest and Umbarger, 1958; Hsia, Knox, Quinn and Paine, 1958; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958), excess, in failure of mental development. The parents must be fully

co-operative and the treatment controlled by serial assessments of phenylalanine in the blood. This is important, as phenylpyruvic acid does not appear in the urine until the concentration of phenylalanine in the blood exceeds 15 mg./100 ml. (Armstrong and Tyler, 1955). Occasionally the introduction of a phenylalanine-restricted diet results in the child going into status epilepticus; a similar state of affairs may occur if, for any reason, the diet has to be stopped.

Where treatment with a phenylalanine-restricted diet is not possible, an attempt may be made to increase the brain concentrations of such amines as 5-hydroxytryptamine and noradrenaline, the formation of which is thought to be inhibited in phenylketonuria (see above). Kirman and his associates suggest that this could be achieved by treating affected children with iproniazid (Pare *et al.*, 1959). This substance inhibits monoamine oxidase, the enzyme responsible for much of the further metabolism of monoamines (Fig. 2) (Blaschko, 1954), and it has been shown, in animals, to increase the brain concentrations of both catechol amines and 5-hydroxytryptamine (Spector, Prockop, Shore and Brodie, 1958).

PATHOLOGY

We were able to trace neuropathological reports of only 20 phenylketonuric cases (Table II) and some of these are exceedingly brief. The brain was stated to be normal in only 3 cases (Cases 2, 3 and 4), but it is possible that other workers, feeling uncertain of the findings, have refrained from publishing their case material. Observations based on unpublished material and lacking enough detail for inclusion in Table II (Jervis, 1954; Norman, 1958) will be mentioned below.

Reduction in the weight of the brain is the commonest and most certain of the recorded anomalies. Taking as normal the brain weights presented by Copoletta and Wolbach (1933), those in Table II are under 90 per cent. in 8, and over 90 per cent. in 2, instances. The weight is not stated in 8 cases and the age not given in 2. Moreover, one of the 2 brains weighing over 90 per cent. of the average (Case 14) is stated by the author to have been "heavy" on account of accumulation of fluid, since its "substance, particularly the white matter, was strikingly underdeveloped", while four of the brains of unstated weight (Cases 6, 7, 8 and 9) were reported to have weighed about two-thirds of the normal. It is also noteworthy that none of the brains exceeded the average weight for the age, and although available information is not sufficiently precise for statistical treatment, there is no doubt that the brains of phenylketonuric patients are mostly small, and this is in keeping with the early observations of Jervis (1937), who found slight microcephaly in 14 of his 18 patients subjected to anthropological measurement. Encephalograms were made in 11 of his cases and several of these presented moderate ventricular dilatation and diffuse increase of subarachnoid air.

The second common anomaly is pallor of myelin staining, present in 7, and absent in 10, of the cases. Of the 3 remaining ones, one (Case 19) is not fully described, one (Case 9) showed absence of myelinated nerve fibres only in the centre of the optic chiasma, the seat of a singular "honeycomb" degeneration, and another (Case 15) presented focal demyelination with fibrous gliosis, thought to be ictal in origin, in one of the occipital lobes. Most of the authors reporting defective myelination interpreted it as evidence of retardation rather than degeneration or atrophy of the myelin, speculating upon its relation to the known biochemical disturbance. It is not easy, however, to be certain

TABLE II

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
1	Penrose (1939)		9 years M	Epileptic idiot.	1,167 1,275	Genital infantilism. Bronchopneumonia. Hydro-nephrosis. Caseous mesenteric gland.	Brain soft and oedematous with a simple pattern of convulsions. Several tense swellings, 0.5-1 cm., present on trunks of both vagi, and smaller ones on most of their branches. Phrenic nerves also slightly affected. Similar nodules in region of pyramidal and near coeliac plexus. Irregular focal hypertrophy of some nerves in the left arm and left sciatic nerve. Histologically, regarded as neurofibromatosis.	
2	Coquet, Myle, Nyssen and Bogaert (1944)		12 years F	Marked mental retardation. Multiple skin eruptions. Terminal pyrexia of obscure origin.		Pulmonary oedema. Fatty change in the liver. Phagocytosis of pigment in the spleen.	Findings thought to be negative. The only abnormality found was a small zone of necrosis in the frontal lobe and slight proliferation of the oligo- and macroglia in the centrum semiovale.	
3	Joseph (1948)	a.		Idiot.	1,200	Tuberculosis.	No abnormality found.	Very incomplete reports.
4	<i>Ibid.</i>	b.		Idiot.	1,200	Tuberculosis.	No abnormality found.	
5	Alvord, Stevenson, Vogel and Engle (1956)	1	16 months M	Epilepsy and low-grade mental retardation. Chronic eczema, many intermittent infections and anaemia. Terminal bronchopneumonia. One sister (Case 2 below) also phenylketonuria.	650 1,010	Oedema and ulceration of scalp. Bronchopneumonia.	Lack of myelin in optic nerves and tracts. Absence of myelin in cortico-spinal tracts. Pallor of myelin-staining in many parts of the occipital lobe, medial longitudinal bundle, brachium conjunctivum, medial lemniscus, commissure of the inferior colliculi and inferior quadrigeminal brachium, middle cerebellar peduncles and transverse pontine fibres. Cervical spinal nerve roots myelinated but pale, with better staining in sacral cord. Incomplete myelination of the 8th cranial nerve. Only traces of myelin in the cauda equina. Perivascular and pericellular oedema. Increase of fat around blood-vessels and in the white matter of the pre-central gyrus with astrocytic proliferation. Faint staining of neurones. Depletion of Purkinje cells.	Autopsy performed 53 hours after death and some of the appearances may possibly be due to autolysis.

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
6	<i>Ibid.</i>	2	5½ years F	Chronic eczema, marked mental retardation, epilepsy. Measles followed by hyper-pyrexia and death. Sibling of Case 1, above		Bilateral interstitial pneumonia.	Brain and spinal cord developed normally. Pallor of myelin with astrocytic proliferation in the optic nerves. Loss of nerve cells and myelin in the paracentral lobule. A little fat around blood-vessels. Loss of Purkinje cells. Pallor of myelin in posterior and antero-lateral columns of the spinal cord and in the cauda equina.	
7	<i>Ibid.</i>	3	67 years			Carcinoma of the thyroid and lipomatosis of the skin.	Neuroglia preparations showed a definite increase in astrocytes. Increase of fat about blood vessels.	Previously seen by Dr. R. M. Stewart who reported paucity of nerve cells and glial excess in the cerebral cortex.
8	<i>Ibid.</i>	4	54 years				Normal myelin staining with gliosis of the cortex and optic chiasma. Increase of fat about blood-vessels.	
9	<i>Ibid.</i>	5	33 years M	Microcephalic idiot.			Normal myelin staining. Astrocytes and microglial proliferation in the cerebral cortex. Increase of fat about blood vessels. "Honeycomb" appearance of optic chiasma with gliosis and a marked loss of myelinated fibres in centre of the optic nerve.	Half of the brain, with cerebellum, weighed 470 g.
10	Larson (1950)	4	20 years F	Idiot.	1,110 1,191	Perforated peptic ulcer.	Cytoarchitectonic anomalies, particularly in area 6 with increased cellular density in fifth and sixth laminae. A few malformed and misplaced cells in the cerebral cortex.	Very brief and incomplete reports.
11	<i>Ibid.</i>	5	21 years F	Idiot.	1,000 1,350	Pulmonary and abdominal tuberculosis.	"Sparse and banal changes of type common in brains of idiots."	
12	Sander (1951) also Klein (1946)		20 years M	Epileptic fit at 1½ years. Microcephalic idiosy with hypopentalism and dwarfing.	1,070 1,450	Miliary tuberculosis. Increased amount fibrous tissue in the middle and posterior lobes of the pituitary.	Slight hemiatrophy of the brain. "Hyalinization" and irregularity in the outlines of the lumina of blood-vessels with "état criblé" most marked in the lenticular subthalamic and red nuclei, and in the substantia nigra. Some perivascular loss of cells. Reduction in the number of Purkinje cells and loss of fibres in the inferior olives.	

Table continued overleaf

TABLE II—*continued*

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
13	Benda (1952), also Mautner and Quinn (1949) (Case 20)	1	21 years F	Idiot with exaggerated knee jerks and undeveloped lobules of the ear	1,135 1,350	Fibrous tuberculosis. Degeneration of eosinophil cells in the anterior and absence of cells in the posterior pituitary. Arachnoidactyly. Thick calvarium.	Marked degeneration with vacuolation of the central white matter of the brain. Perivascular fibrosis with some hyalinization of some blood vessels. Degeneration of white matter in external capsule, claustrum and the centre of the temporal lobe. Demyelination of the fronto-pontine fibres. Amyloid and myelin bodies present in the globus pallidus. Lack of myelin in the centrum and folia of the cerebellum. Degeneration of the reticular substance of the medulla and the granular layer of the cerebellum.	
14	<i>Ibid.</i> Case 22 of Mautner and Quinn (1949)	2	21 years M	Idiot with attacks of "nodding and shaking"; at times momentary loss of consciousness. Two siblings probably had phenylketonuria.	1,360 1,450	Pulmonary tuberculosis. Chronic hepatitis.	Degeneration of white matter as in Case 1 above. The centrum semiovale is small and grey in the myelin preparations. The digital white matter is very thin. Demyelination of the cerebellum and fronto-pontine fibres. Paucity of cortical nerve cells. The spinal cord is small, narrow and under-developed. Amyloid metachromatic bodies in the white matter of the spinal cord.	The author observed that the weight of the brain must have been due to accumulation of fluid, since the substance, particularly the white matter, was strikingly under-developed.
15	Corseillis (1953)	R.C.	25 years F	Epileptic idiot with slight spasticity of lower limbs and clumsiness and inco-ordination of voluntary movements. Absence of ear lobules. Obscure terminal pyrexial illness. Two siblings were also phenylketonuric.	1,175 1,350	Mild myocardial and hepatic degeneration. Skull cap unusually thick.	Retrograde degeneration or pellagra-like change in Betz cells and neurones of striatum, mamillary bodies, reticular substance, many pontine cells, nucleus ambiguus, dorsal nucleus of the vagus, cuneate nucleus, and a few anterior horn cells of the cervical and thoracic segments of the spinal cord. Marginal gliosis of the cerebral cortex. Walls of perforating blood-vessels prominent showing some hyalinization. Patches of demyelination and heavy gliosis in right occipital lobe. Slight paucity of cells in the Sommer sector of the hippocampus. Small amount of pigment in the substantia nigra. Slight focal meningeal haemorrhage over cerebellum with subjacent necrosis.	

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
16	Leoni (1953)		20 years M	Mental retardation and paralysis following attack of meningo-encephalitis in early infancy. Flexion contractures of lower limbs. Cranio-facial asymmetry.		Single kidney and adrenal. Hepatomegaly. Bronchopneumonia.	Small occipital lobes and abnormal shape of posterior horn of the lateral ventricles. Cytoarchitectonic anomaly of area 4. Some focal pallor of myelin staining and cellular loss in the cerebral cortex and corpus striatum.	
17	Bonfiglio (1954)	Case II	7 years M	Mental retardation with epilepsy commencing at 10 months, lasting a year, and not recurring since.	1,060 1,263	Adhesive pericarditis and pulmonary tuberculosis.	Thickening of the meninges. Atrophy and loss of nerve cells, particularly in the anterior portion of the brain, Betz cells being particularly affected. Astrocytic proliferation in the transitional zone between grey and white matter. Hypertrophy of some blood vessels. Increase of oligodendrocytes in the white matter. Myelin normal. Some loss of Purkinje cells.	
18	Scholz (1957)		23 months F	Severe mental deficiency with terminal epilepsy. Pulmonary tuberculosis.	825 1,064	Primary T.B. complex. Anaemic areas in kidneys and heart. Enlargement and fatty change of liver.	Anomaly of nuclear chromatin in nerve cells consisting of pallor of nucleolus and dispersion of dark particles of chromatin throughout nucleus. Peripheral chromatolysis. This change is found in about half of the cortical pyramidal cells, in most of the thalamic neurones, corpus striatum, and to a lesser extent in the Purkinje cells and vegetative centres. Retardation of myelination in the centrum semiovale, anterior commissure, internal capsule, pontocerebellar fibres, central zone of corticopontine fibres, the pila and periphery of the superior olives, lateral columns of the spinal cord and Helweg's tract. Fibrous gliosis of the cerebrium and cerebellum increasing caudad.	The author considers that the state of myelination is that of a normal 5-month old child.
19	Fellman (1958)		14 years				Hypopigmentation of the substantia nigra and locus caeruleus.	Full neuropathological report to follow.
20	Poser and Bogaert (1959)		18 years M	Mental defective with I.Q. = 30. Severe intractable epilepsy with frequent status epilepticus.		Lobular and aspiration pneumonia.	A few foci of necrosis, possibly ictal in origin. Areas of pallor of myelin-staining with fibrous gliosis in centrum semiovale, corpus callosum, periventricular white matter, cerebellar white matter, hilum of dentate nucleus and optic tracts. More severe lesions in arcuate fibres of the inferior olives, olivo-cerebellar and vestibular tracts and in the dorso-lateral portion of the medulla.	

about pallor of myelin staining if it is slight and unaccompanied by evidence of myelin breakdown or other reactive change. It is true that some of the authors have also reported a certain amount of associated glial proliferation, but this again may be somewhat subjective. Among the comments not tabulated here Jervis (1954) mentions that he examined 5 cases for histological evidence of myelin change. In three, all adults, no demyelination was found; in the fourth, a boy aged 3, there was some paleness of myelin in the temporal region. The fifth presented a curious and probably fortuitous association with Schilder's disease which commenced at the age of 25. Pallor of myelin in the celloidin-embedded material of one of his cases was found by Norman but the myelin stained normally in frozen Kulschitzky-Pal sections.

Phenylketonuria seems to be rarely associated with frank neural or somatic malformation. Peripheral neurofibromatosis was present in Case 1, and a single kidney in Case 16, the latter case showing also smallness of occipital lobes with abnormal shape of the posterior horns of the lateral ventricles. The occurrence of micropolygyria in one of his unpublished cases is mentioned by Norman.

A pellagra-like retrograde neuronal change was reported in one instance (Case 15) and a neuronal nuclear anomaly in another (Case 18). Hypopigmentation of the substantia nigra and locus caeruleus was described in Case 19, but it is difficult to be sure of its significance without comparison with an adequate number of normal controls. It is noteworthy in this connection that the substantia nigra and locus caeruleus are normally pigmented in albinos (Foley and Baxter, 1958) and the pigment is probably not formed, as in the skin, by the tyrosine-tyrosinase system.

The apparent inconstancy of the morphological changes is in contrast to the persistent biochemical disturbance and this has been commented upon by some of the authors (Peters, 1958). Poser and Bogaert (1959) relate this to the wide difference in the level of intelligence known to occur in phenylpyruvic cases. However, it is difficult to accept this interpretation since few, if any, pathological reports of the higher-grade phenylketonuric patients have been published and all the cases listed in Table II appear to be of idiot or imbecile range of mentality.

It is somewhat strange that more attention has not been given in the past to the one constant and certain feature of phenylketonuria, viz., the tendency to microcephaly and micrencephaly.

As a basis for further discussion, we present below the clinical and pathological findings in 4 cases of phenylketonuria which have come to autopsy at the Fountain Hospital. Three were admitted for inclusion in a clinical trial with 5-hydroxytryptophan (Kirman, Pare, Sandler and Stacey, unpublished). The fourth (Case 1 below), had been studied earlier.

The histological methods employed were similar in all cases. After prolonged fixation in formol saline, representative blocks of all cerebral lobes, basal ganglia, optic nerves, brain-stem and spinal cord were embedded in celloidin and in paraffin. The celloidin sections were stained with cresyl violet, Heidenhain's haematoxylin and the Adams method for myelin (Adams, 1959), haematoxylin and Van Gieson, by the Holzer method for fibrous glia, and with phosphotungstic acid and haematoxylin. Paraffin sections were stained with haematoxylin and eosin and Van Gieson. Frozen sections were treated by the Herxheimer method for fat, the Holzer method, the del Río-Hortega's method for astrocytes, Penfield's modification of del Río-Hortega's method for microglia and the original as well as the Gros modification of Bielschowsky's

method for neurofibrils. Blocks of somatic tissue were embedded in paraffin and treated by the customary histological techniques. All neural material was compared with tissue of normal controls of approximately the same age, treated in a similar way. Blocks of the brains were also sent to Dr. G. H. Sloane-Stanley for a chemical estimation of myelin by the galactose method. It is hoped to publish the results of this investigation later.

Case I. D.G.O.

Two maternal cousins of this boy were certified mental defectives but a very careful enquiry by Dr. Renwick elicited no proved cases of phenylketonuria in the family. There is no consanguinity in the family. The patient's one older brother has a cleft palate.

His father was 34 and mother 26 years old at the time of the patient's birth, which took place at full term after a normal pregnancy. Early infancy was uneventful, but by the 6th month he was noticed to be slow and lethargic, and this was at first attributed to fatness. On account of weight and helplessness he became increasingly a burden at home and was admitted to the Fountain Hospital at 4½ years. His weight then was 19 kg. with height—96.2 cm., and head circumference—51.8 cm. He was fair and blue-eyed. Other tests were non-contributory. There was a circumoral salivary rash and some roughening of the skin over the extremities. All tendon jerks appeared to be normal.

He was a large placid child who would seize objects and put them to his mouth without curiosity or manipulation. He could stand but not walk unaided, had no sphincter control and was unable to eat solid food. He could follow a rattle with his eyes and reach for it when left by himself, but showed little other spontaneous activity, sitting about all day, gurgling, and opening and closing his fists aimlessly. His developmental age on the Vineland Maturity Scale was 9 months, and he was considered to be of idiot level. The urine of this case was positive for phenylpyruvic acid in a single test done on the ward, which unfortunately was not repeated.

He died from broncho-pneumonia a month after admission.

Pathological Findings

The brain weighed 1,360 g. and showed no macroscopic abnormality. Histologically, no definite abnormality was seen in any part of the central nervous system.

Less certain changes included the following: slight diffuse deficiency in the number of cortical neurons was possibly present in many areas including the Sommer sector of the hippocampus. Some of the remaining cells showed shrinkage and many "ghost" forms were also present. Indistinctly demarcated areas of pallor in myelin staining of both celloidin embedded and frozen sections of the kind described in some of the previously reported cases of phenylketonuria were present in the centrum semiovale (Fig. 3). Similar appearances could be produced in the control material and the significance of the findings seems thus uncertain. The cerebellar white matter showed comparable pallor of myelin staining, and there was possible slight loss of Purkinje cells. Individual myelin sheaths and axis cylinders in the "pale" areas showed no abnormality of staining when viewed under high magnification. The long fibre tracts in the brain-stem and spinal cord also stained normally for myelin but showed considerable vacuolation of interstitial tissue (Fig. 4). No fibrous gliosis or glial hyperplasia was demonstrable anywhere by the Holzer and the silver impregnation methods.

A few of the cells in the substantia nigra showed early slight pigmentation, and this was more marked in the locus caeruleus. Comparison with control material showed no appreciable retardation in the degree of this pigmentation.

The only significant abnormality outside the nervous system was broncho-pneumonia, the lungs showing foci of alveolar consolidation and of lobular collapse. The following other organs were examined histologically: the heart, skeletal muscle, thyroid, kidney, small intestine, thymus, adrenals, pituitary

and the testis. The liver showed a moderate amount of fatty change, more marked in the centre of the lobules. Other organs were normal.

Case II. J.P.

This boy was the third child of a mother aged 27 and father 28 at his birth. The 2 older siblings are normal. A younger sibling was expected in 1958 but no details about his state of health are as yet available.

The patient was a full-term baby, born at home and weighing 2.8 kg. Pregnancy was quite normal and, although the birth was said to be precipitate, there was no obvious evidence in the immediate neonatal period of damage having occurred to the child. Slowness of development became apparent at 9 months and phenylketonuria was diagnosed at 13 months. The paediatrician observed at that time that he was quiet and passive, making no response to examination. He did not reach for objects and took no interest in toys placed before him. He would not turn his head towards noises or lights; could not sit up or hold up his head consistently. Phenylalanine-free diet brought with it a somewhat doubtful improvement.

He was admitted at 19 months to the Fountain Hospital, for inclusion in a trial of 5-hydroxytryptophan (Kirman, Pare, Sandler and Stacey, unpublished).

The psychologist (Mrs. L. Mundy) assessed his mental age on the Griffith Mental Development Scale as 19 weeks with an I.Q. of 23. He appeared thus to be of low imbecile level, and showed little variation in the various developmental aspects, though that of speech was the lowest. Physically, he was a pale, delicate, fairly well-nourished baby. His head circumference measured $16\frac{1}{2}$ inches (41.8 cm.) (normal 48.8 with S.D. ± 1.1), so that he was well within the microcephalic range. The anterior fontanelle could not be palpated. He was unable to walk, stand or sit up, but could lift his head off the pillow, smiled occasionally and seemed pleased when given attention. He did not reach for objects but clenched a pencil when it was placed in his hand. His muscle tone was low, but no focal neurological signs could be elicited. The EEG report (Dr. D. A. Pond) reads: "One grain of 'seconal' produced a satisfactory sleep record. The barbiturate fast activity is not prominent but the slow rhythms are regular and symmetrical."

Estimations of serum 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in early morning urine showed values of 190 ng./ml. (1 ng. = 10^{-9} g.) and 4.2 mg./g. creatinine respectively.

A few months after admission, the patient developed diarrhoea, from which he recovered. This recurred again when he was 2 years old in a more severe form and he died a week later.

Pathological Findings

The brain weighed 737 g., the average normal for this age being 1,064 g. It presented no external abnormality. The coronal blocks of the cerebrum showed possible slight diminution in the amount of white matter. Transverse sections through the subcerebral formations were macroscopically normal.

The unequivocal histological abnormalities in this case consisted of diffuse fibrous gliosis of the white matter of the centrum semiovale (Fig. 5), and a small focus of post-necrotic scarring in the cerebellum (Fig. 6).

The diffuse cerebral gliosis was easily seen on naked-eye examination of the histological preparations, presenting as a dense network of glial fibres on higher magnification (Fig. 7). This density was uniform centrally, showing some accentuation in the juxta-cortical areas. The cells concerned were mostly fibrillary astrocytes. The number of swollen-bodied cells or of microglia was not increased. There was also no discernible pallor of myelin in the appropriately stained sections, or evidence of past or continued myelin degeneration in the form of sudanophil debris or structural abnormality of myelin sheaths. A small number of fat-containing compound granular corpuscles was present, however, around a few of the blood vessels.

The areas of cerebellar scarring were situated superficially on two adjoining folia of the uvula and pyramid, the affected tissue showing atrophy of the molecular and Purkinje cell layers with astrocytic replacement.

The less certain findings were as follows: glial cells showed a slight increase in the molecular layer of the cerebral cortex, and there was a possible loss of neurons in layer III, particularly of the frontal lobes. Slight neuronal loss was also present in the Sommer sector of the hippocampus. Some gliosis with an

excess of syncytial astrocytes was present around the ventricles, especially the fourth. There was excess of fibrous glia in the grey matter at all levels of the spinal cord.

Although histological evidence of past or present myelin degeneration was lacking in the gliosed centrum semiovale, naked-eye comparison of the section with normal controls suggested that the total amount of the white matter was somewhat deficient.

As in the controls, no pigmentation could be detected in the substantia nigra and locus caeruleus.

Other Organs. The lungs showed areas of bilateral basal collapse, more marked on the left side. Areas of collapse were also present in the right upper lobe. Veins draining the lower parts of both kidneys showed ante-mortem thrombosis and the tissue drained by them was greatly congested. The testes were in the inguinal canals. The pituitary weighed 0.17 g. and the thyroid 1.5 g.

The following organs were examined histologically: kidneys, small intestine, eyes, heart, spleen, liver, lung, pancreas, dural sinus, bone-marrow, adrenal, testes, thymus, thyroid and pituitary.

The *eyes* showed no detectable reduction of pigment in the retina, choroid or posterior layers of the iris. There was, however, lack of pigmented chromatophores in the iridial stroma. The *adrenals* presented a sharp contrast between the lipoid-rich zona glomerulosa and the rest of the cortex. The *kidneys* showed considerable congestion with recent ante-mortem thrombosis of some of the renal veins. In the *lungs* there was some suppurative bronchiolitis and early bronchopneumonia, together with widespread complete and incomplete pulmonary collapse. Other organs showed no noteworthy change.

Case III. B.N.

There is no family history of mental or neurological disease apart from fits during the childhood of one paternal uncle which did not recur in later life. The mother's first pregnancy resulted in a miscarriage. The oldest living child has cerebral palsy but not phenylketonuria; the next child is normal, and the patient was the third of the liveborn children. The father was 27 and mother 23 years old at the birth of the patient. After a normal pregnancy, the baby was born spontaneously by the vertex at the 37th week of gestation. His birth weight was 3 kg. and his condition during and after birth was considered normal.

His normal development was retarded; at 11 months he was still unable to sit up on his own. At 1 year he could hold up his head and at that time began having epileptiform fits. He was thought to be deaf. Phenylketonuria was diagnosed at 13 months. The head circumference at 15 months measured 43.9 cm., the average normal for the age being 48.8 cm. with S.D. ± 1.1 . Thus he was grossly microcephalic. He had an iron deficiency anaemia with Hb of 75 per cent. (Haldane). He was having then many petit mal attacks, and the EEG report was as follows: "slow waves and occasional spikes were recorded from both hemispheres. The slow waves had a frequency of 3 per second. The abnormalities were diffuse, no one region being the predominant generator." His motor development quotient was 34.

The child was admitted at 15 months to the Fountain Hospital for trial with 5-hydroxytryptophan.

In the first month of his stay at this hospital, he had 5 petit mal attacks but none occurred later. His mental age was assessed at 15½ weeks, with an I.Q. of 20 on the Griffiths Mental Development Scale. No abnormality was seen on ophthalmological examination. The jaw-jerk was brisk and there was no facial weakness. A blink reflex was present to very loud noise, with no response to other sounds. The tongue showed occasional quivering and central bunching. The upper limbs were flaccid on passive movement with, however, marked briskness of tendon jerks; occasionally both arms were outstretched with the hands clenched and the arms exhibited a rapid "shivery" tremor. The abdominal reflexes were absent. The lower limbs were held in abduction at the hips and moderate flexion at the knees. They were immobile in comparison with the arms, and hypotonic. The tendon jerks were present and equal, and the plantar responses were flexor. The muscles seemed wasted beneath the fat. Placing and supporting reactions were absent in upper and lower limbs.

An EEG done a month after admission under chloral hydrate (Dr. D. A. Pond) showed symmetrical fast and slow activity and there were in addition low voltage spikes and spike

and wave complexes seen independently on the right and left sides. The amplitude of all activity was much larger in the posterior than the frontal area.

At the same time, the child developed diarrhoea which lasted 3 weeks. No pathogens were isolated from several specimens of the stool.

There were 63 mg. 5-hydroxytryptamine/ml. serum and 1.8 mg. 5-hydroxyindoleacetic acid/g. creatinine in early morning urine.

A blood count taken 2 months after admission showed Hb—10.2 g./100 ml. (69 per cent.) C. The W.B.C. were 10,800/c.mm.

Five months after admission, the diarrhoea recurred. Pathogens were again not found in the stool but, in spite of treatment, the patient died a week after the onset of the symptoms.

Pathological Findings

The C.N.S. The head circumference at post-mortem was 45.4 cm., the average normal for the age being 49.6 cm. with S.D. = ± 1.2 .

The complete brain weighed 871 g., with the cerebellum together with the brain-stem weighing 120 g. (The average normal for the age is 1,050 g.)

The superficial veins were greatly congested and an area of terminal subarachnoid haemorrhage, 2.5×1 cm., was present over the right inferior frontal gyrus. All ventricles were moderately dilated, and the floor of the 3rd ventricle was thin. Coronal blocks of the cerebrum showed slight reduction in the thickness of the corpus callosum and the centrum semiovale.

Histological preparations presented on naked-eye examination generalized diffuse fibrous gliosis of the cerebral and cerebellar white matter. Higher magnification showed an increase of fibrous astrocytes with a dense network of glial fibres. There was, however, no unequivocal evidence of corresponding loss of myelin. The white matter stained normally in most areas and myelin sheaths showed no evidence of past or continued degeneration, but, as mentioned above, the total amount of white matter was probably smaller than normal. In addition, a few small foci of definite myelin loss (Fig. 8) with astrocytic replacement were seen in the white matter of the frontal lobe.

Less certain histological abnormalities were as follows: the thickness of the cerebral cortex seemed reduced in some areas, particularly at the bottom of the sulci, and there was some neuronal paucity in the superficial cortical laminae. Perivascular cellular loss was also present in the cerebral grey matter (Fig. 9). The molecular layer showed some glial hyperplasia and a curious feature was microglial proliferation in layer 2 of the fusiform gyrus (Fig. 10). A lesser degree of microglial excess could also be seen in the superficial layers of many other cortical areas. A few ependymal granulations were present in the posterior horns of the lateral ventricles. There was some marginal and periventricular fibrous gliosis of the brain and brain-stem and syncytial astrocytes were present for some distance around the ventricles in the periventricular grey matter. The only abnormality in the spinal cord was fibrous gliosis without apparent parenchymal loss in the anterior horns of the grey matter. The Bergmann glia were increased in the cerebellum, some Purkinje cells had disappeared, and a few showed "homogenizing cell change" (Fig. 11).

Neutral fat was present in only a few compound granular corpuscles around some of the blood vessels.

The substantia nigra and locus caeruleus were unpigmented.

Somatic Organs. The trachea and main bronchi contained purulent secretion, and pleural adhesions were present over the right lower lobe. Yellowish, gritty particles of gravel were present in the renal pelvis. The teeth were carious. The jejunum and colon were somewhat indurated and leathery in consistency, and the intestinal mucosa showed areas of congestion and possible inflammation. The pituitary weighed 0.15 g. and the thyroid 1.75 g.

The following organs were examined histologically: eyes, spleen, small and large intestine, adrenals, pituitary, bone-marrow, pancreas, thyroid, salivary gland, thymus, liver, lungs and testes.

The eyes showed no apparent lack of retinal or choroidal pigment. The posterior layers of the iris were likewise well pigmented, but there was no pigment in the chromatophores of the iridial stroma. The *lipoid-rich* zona glomerulosa of the adrenals was sharply demarcated from the sub-joining lipoid-poor cortex (Fig. 12). The liver showed diffuse fatty change, somewhat accentuated towards the lobular periphery. There was marked increase in the amount of submucosal tissue in the small and large intestine. It formed a dense layer, equalling in places the thickness of the muscularis and consisting of sparsely cellular cylindrical structures (Fig. 13). The material stained slightly more bluish with haematoxylin than the usual collagen, giving in some areas the appearance of almost cartilaginous hyaline tissue. It was fuchsinophil with the Van Gieson stain. The innermost parts of the intestinal mucosa were necrotic and denuded in some places. Most of the pulmonary tissue examined showed collapse with purulent bronchiolitis and early bronchopneumonia. Some areas showed ante-mortem thrombosis of the pulmonary veins with intense capillary engorgement. The only histological change in the kidneys was the presence of a few partially calcified casts in the collecting tubules.

Case IV. H.H.

The patient was the issue of the last of four pregnancies, the first of which had ended in miscarriage. One of the two living siblings suffers from pulmonary tuberculosis. The family is free from mental defect, phenylketonuria or consanguinity.

In the fifth month of the patient's gestation, the mother was found to have pulmonary tuberculosis; in addition there was said to be a threatened abortion at 3-4 months. However, the pregnancy proceeded to term, the birth was normal and the baby weighed 2.8 kg. General retardation of his development became obvious at 7 months and he is said to have had epilepsy. Phenylketonuria was diagnosed on admission to hospital at 10 months, and an EEG taken at that time was said to be typical of myoclonic epilepsy. The fits were said to be controlled by "Diamox"—250 mg. b.d. He was started on a phenylalanine-restricted diet but it was difficult to get him to eat it; his weight remained stationary and after 2 months, in spite of some improvement in his mental state, the diet was discontinued.

At one year he was admitted to the Fountain Hospital for inclusion in the clinical trial of 5-hydroxytryptophan, but had not received this substance prior to death.

At the time of admission, he was described as a blond, rather pale child with broad, widely-spaced upper incisor teeth. His skull was slightly asymmetrical and the head circumference measured 44.7 cm., the average normal for the age being 47.1 cm. with S.D. ± 1.3 . He showed slight hypotonia but no other neurological signs. "Diamox" was discontinued but no epileptic fits recurred. Several EEG records (Dr. D. A. Pond) showed symmetrical high voltage delta activity and low voltage fast activity, regarded as normal for age and drug effects. The serum total proteins measured 7.2 g./100 ml. and lipids 625 mg./100 ml. (Dr. J. Stern), these values being within the normal range.

Estimation of 5-hydroxytryptamine in the serum and 5-hydroxyindoleacetic acid in the early morning urine gave values of 140 ng./ml. and 1.4 mg./g. creatinine respectively.

His intelligence was estimated carefully on several occasions. Early after admission he was thought to be of imbecile level and no significant change was observed when the progress was last assessed some 6 months later.

He had recurrent attacks of respiratory and intestinal infection during his stay in hospital, succumbing to one of these at 1 year 8 months.

Pathological Findings

The brain weighed 870 g., the average normal for the age being 1,050 g. The right cerebral hemisphere projected slightly forward in keeping with the contours of the skull, but there was no gyral abnormality. The coronal blocks of the cerebrum and transverse sections of the brain-stem and spinal cord were also macroscopically normal.

The only certain histological abnormality was slight or moderate fibrous gliosis of the white matter in the frontal and temporal lobes.

Less certain findings consisted of the following: slight pallor of myelin staining was present in the temporal lobes and the lower portion of the external capsule. Elsewhere myelin stained normally, but the total amount of the white matter in the centrum semiovale was probably reduced. Subpial fibrous gliosis was widespread over the cerebral cortex and periventricular gliosis was present around the ventricles, particularly the 4th, where many syncytial hyperplastic astrocytes ("Gliarosen") were situated in the periventricular grey matter external to the zone of fibrous gliosis (Fig. 14). Slight deficiency in the numbers of cortical neurones was present in many cerebral areas (Fig. 15). The white and grey matter of the brain-stem presented considerable vacuolation, but there was no excess of neutral fat or other evidence of past or continued degeneration of myelin.

Cells in the substantia nigra and locus caeruleus showed no pigmentation, but this was also the case in the control material. Some fibrous gliosis was present in the grey matter of the spinal cord.

Other Organs. The lungs showed basal congestion with a narrow rim of marginal collapse and a few small areas of lobular collapse. The pituitary weighed 0.3 g., and the thyroid 2.7 g.

The following organs were examined histologically: spleen, kidney, testes, salivary glands, small intestine, thyroid, thymus, adrenals, heart, lungs, 3 parathyroids and bone-marrow.

The *lungs* showed areas of collapse and a variable amount of oedema. The mucosal epithelium of the *small intestine* was partially denuded and the lymphoid tissue of the Peyer's patches was oedematous. Follicles at the periphery of the *thyroid* gland contained colloid; centrally, they were devoid of it, the tissue consisting of solidly arranged cells filling the lobules. The amount of fatty tissue in the *parathyroids* was possibly excessive. Their glandular parenchyma was formed entirely by "chief" cells without any acidophil or "wasserhelle" elements. Granular and hyaline casts were present in the collecting tubules of the *kidney*, which also showed some desquamation of the epithelium. The zona glomerulosa of the adrenals contained much lipid and was sharply demarcated from the subjoining zona fasciculata and reticularis which had little lipid. Other organs showed no noteworthy change.

DISCUSSION

Save for Case I, whose phenylketonuria was perhaps doubtful, all brains in this series showed some micrencephaly weighing 69 per cent. of the average normal in Case II and 83 per cent. in Cases III and IV. Case III showed in addition moderate ventricular dilatation.

The presence of defective myelination, as shown by pallor of myelin staining, is more doubtful. There was slight pallor of the temporal lobe and external capsule in Case IV, and a few small foci of demyelination were present in the frontal lobe of Case III. Defective myelination could neither be confirmed or excluded in other areas or cases. On the other hand, all the 3 micrencephalic brains showed diffuse fibrous gliosis of the white matter of the centrum semiovale and its digital extensions with probable reduction in the total bulk of the white matter. It is possible therefore that in cases showing no definite pallor, individual normally-staining fibres had been condensed to normal proximity with each other by the associated scarring. The concomitant slight



FIG. 3.—Case I. Occipital lobe showing pallor of myelin in the central white matter.
Heidenhain $\times 2\frac{1}{2}$.



FIG. 4.—Case I. Vacuolation of tissue in the reticular substance of the pons. Heidenhain $\times 150$.

[face p. 880.



FIG. 5.—Case II. Occipital lobe. Heidenhain, left; Holzer, right. Fibrous gliosis of the central white matter. $\times 2\frac{1}{2}$.

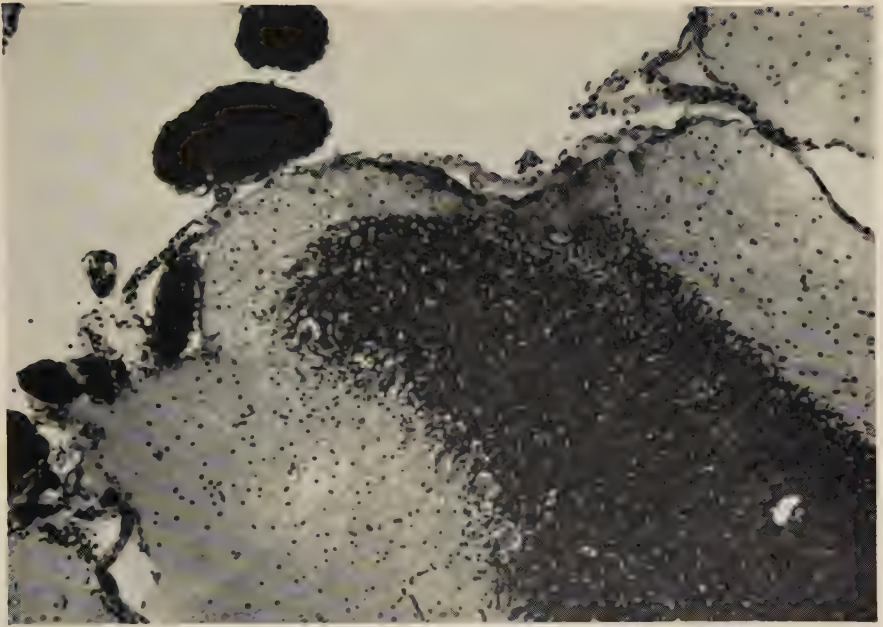


FIG. 6.—Case II. Gliotic focus in the cerebellum. P.T.A.H. $\times 125$.

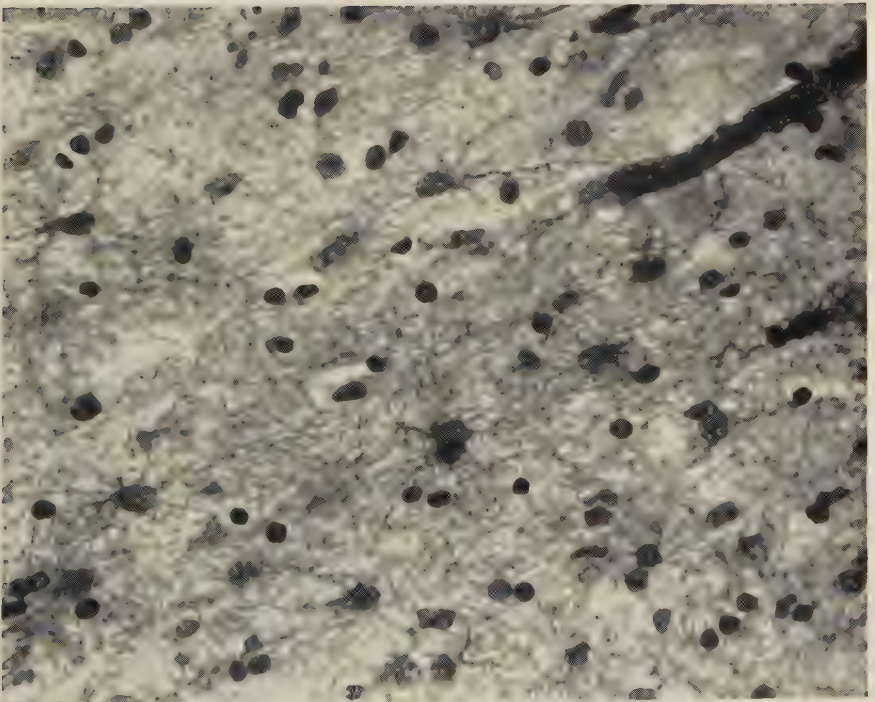


FIG. 7.—Case II. Gliosis of central white matter. Holzer $\times 500$.



FIG. 8.—Case III. Frontal lobe with small foci of myelin loss. Heidenhain $\times 2\frac{1}{2}$.



FIG. 9.—Case III. Perivascular cellular loss. Cresyl violet $\times 150$.

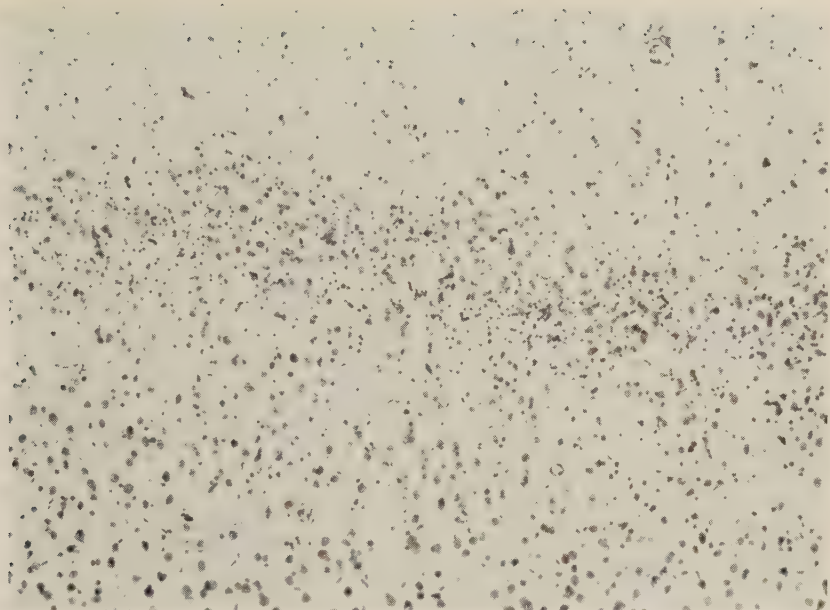


FIG. 10.—Case III. Fusiform gyrus. Microglial proliferation in layer 2. Cresyl violet $\times 125$.



FIG. 11.—Case III. Loss of Purkinje cells in cerebellum. Cresyl violet $\times 150$.

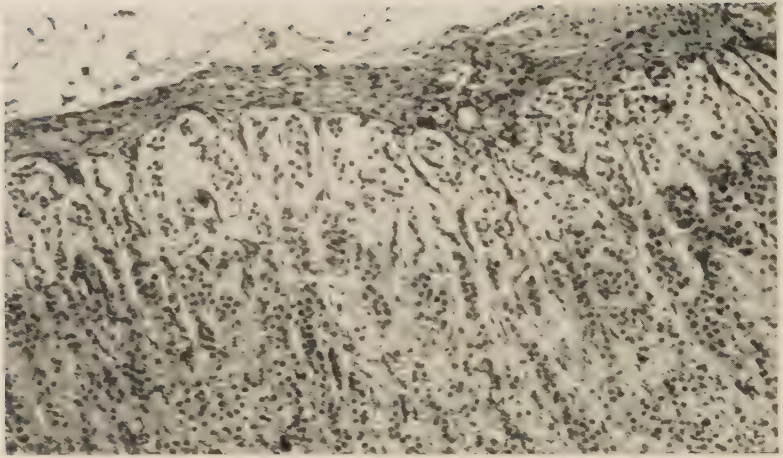


FIG. 12.—Case III. Adrenal showing sharp demarcation of zona glomerulosa from subjoining cortex. H. and E. $\times 150$.

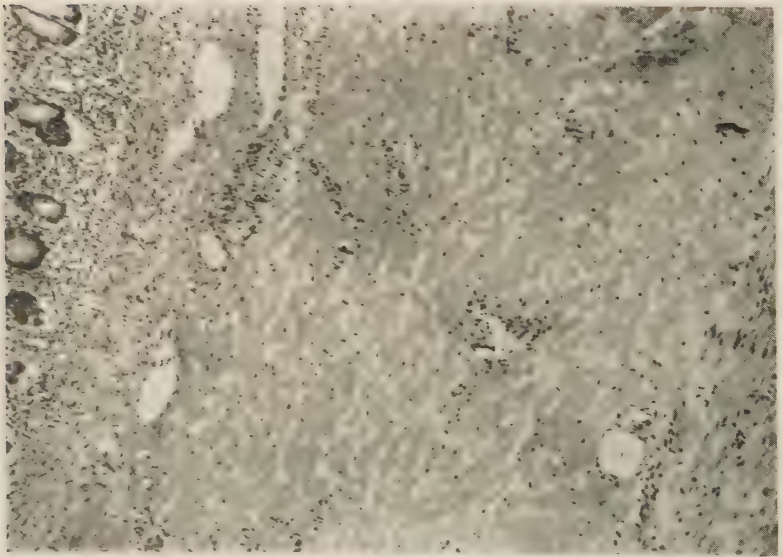


FIG. 13.—Case III. Small intestine with adventitious tissue in the submucosal layer. H and E $\times 150$.

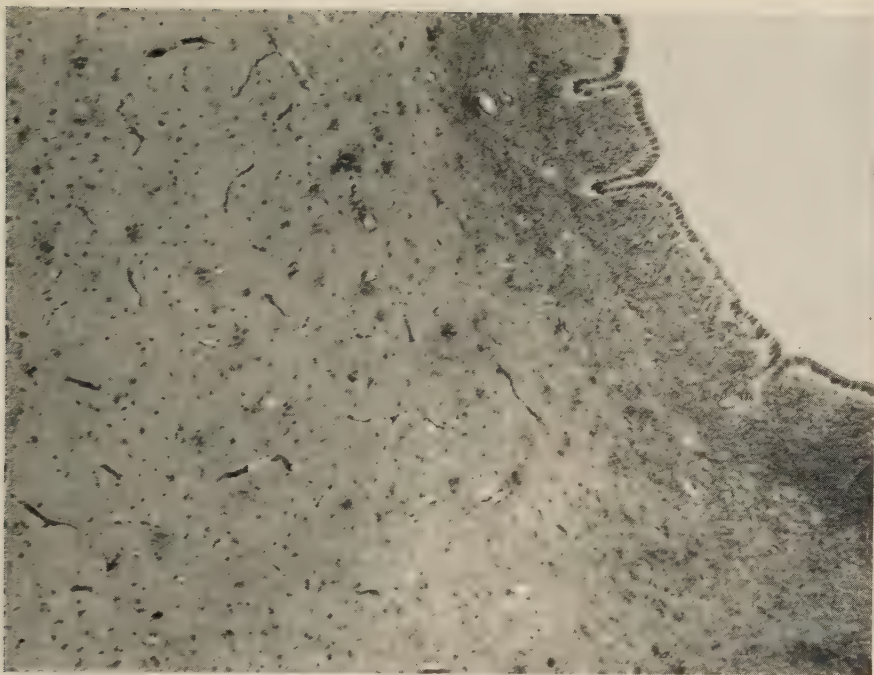


FIG. 14.—Case IV. Periventricular gliosis in the pons. P.T.A.H. $\times 150$.

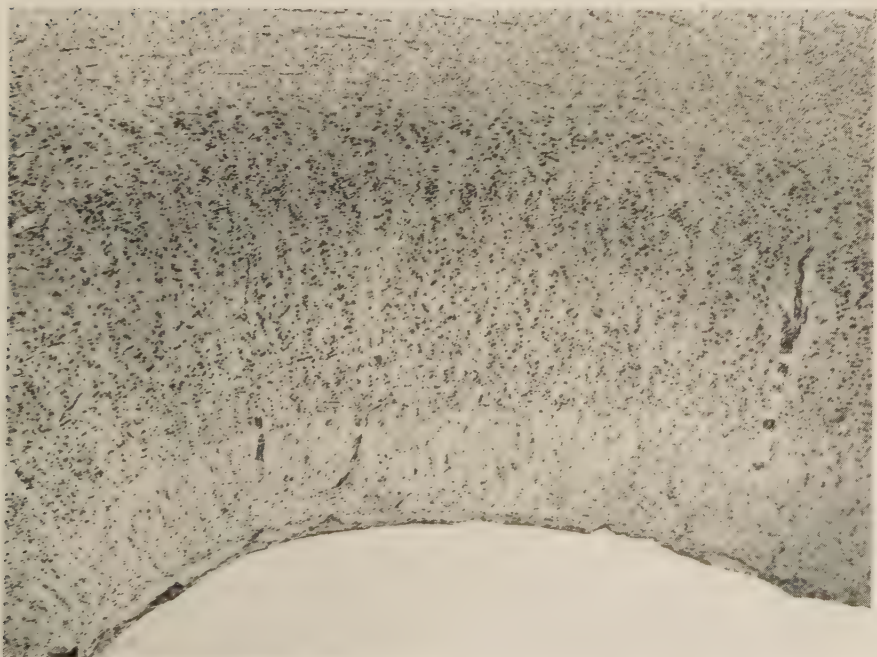


FIG. 15.—Case IV. Cingulate gyrus showing slight neuronal loss. Cresyl violet $\times 150$.

paucity of nerve cells and absence of gross myelin breakdown suggest that the change had involved entire neurons or areas and that the pathogenetic process is not selectively myelinoclastic.

Diffuse gliosis of the white matter with little or no apparent loss of myelin is common in low-grade mental defectives, particularly if they are micrencephalic. It was first described by Freeman (1927) in 4 cases of microcephaly. Meyer and Cook (1937) were also impressed by its frequency in the brains of 22 mental defectives examined by them. In a later study, Meyer and Jones (1939) found it in 10 out of 15 cases of mongolism. The condition is therefore non-specific, signifying, possibly, the result of different processes ending in non-development or disappearance of neurons and their axons with condensation of the remaining ones.

Pending further study, these changes must be regarded as inconstant in phenylketonuria. However, some of the brains in Table II may well have shown similar changes, and this applies particularly to Cases 3, 18 and 20. Only the use of identical methods by different workers could ensure verification of their frequency.

It is not yet possible to determine the time of onset of the morphological changes. Micrencephaly does not necessarily imply prenatal onset; the head circumference of many microcephalic children is within normal limits at birth, and this may be so in phenylketonuria. Rarity of associated neural or somatic malformations in this condition also suggests that the morphological changes do not commence in early gestation. Biochemical evidence (Armstrong and Binkley, 1956) certainly suggests that the baby is normal at birth and this is supported by the clinical picture (see above). That irreversible changes of a diffuse gliotic type associated with micrencephaly do develop, however, is also in line with clinical experience, especially when it comes to treatment. Generally speaking, a phenylalanine-restricted diet is most likely to be effective when started in the first few months of life but may be worth trying up to the age of 3 or 4 years if the I.Q. is 40 or higher (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). Children over this age, especially if they have an I.Q. of less than 20, are unlikely to receive much benefit from dietary treatment. It would appear that, following separation from the mother and the protection which her liver affords, changes occur in the phenylketonuric's brain which not only prevent the normal development of intelligence, but which rapidly become irreversible in the absence of effective treatment. Thus, the morphological considerations do not preclude arrest or reversibility of pathogenesis, but rather emphasize the need for early and effective treatment. Efforts should be made to find a simpler and more reliable treatment based on further biochemical studies.

SUMMARY

Following a general review of the literature, the neuropathological features of four phenylketonuric cases are presented. Micrencephaly and fibrous gliosis of the white matter were the main findings, but slight pallor of myelin staining was also demonstrated in two of the cases.

The neuropathological, clinical and biochemical findings in phenylketonuria are compatible with the view that irreversible changes occur in the brain, but may only develop postnatally. This emphasizes the need for early and effective treatment.

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Cases II, III and IV were referred to the Fountain Hospital by Dr. A. W. Abramson, Dr. J. W. Farquhar and Professor A. G. Watkins, for inclusion in a therapeutic trial.

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BLOOD PLATELET 5-HYDROXYTRYPTAMINE LEVELS IN PSYCHIATRIC PATIENTS

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INTRODUCTION

THE interest of 5-hydroxytryptamine (5HT) for psychiatry arose originally from Gaddum's (8, 9) observation that its peripheral pharmacological actions were antagonized in a highly specific manner by a low concentration of lysergic acid diethylamide (LSD). This led to the hypothesis that the hallucinogenic action of LSD was due to its antagonism to 5HT in the central nervous system (Woolley and Shaw, 21; Gaddum, 7). However, Cerletti and Rothlin (5) subsequently found that brom-LSD, which is not a hallucinogen, was an equally potent antagonist of the peripheral actions of 5HT.

Brodie and his colleagues (3, 15, 16, 18) observed that reserpine depleted the body of its stores of 5HT, and ascribed the tranquillizing action of reserpine to interference with the 5HT binding sites in the brain, giving a continuous liberation of endogenously synthesized 5HT. It has however subsequently been observed that reserpine depletes the body of its stored noradrenaline in a quantitatively similar manner (Paasonen and Vogt, 13; Brodie *et al.*, 2).

Other drugs recently introduced to psychiatric practice also affect the blood platelet 5HT level in therapeutic dosage. Iproniazid ("Marsilid") raises the level (Pletscher and Bernstein, 14), and this can be ascribed to its known power to inhibit amine oxidase, which destroys 5HT. Imipramine ("Tofranil") lowers the level, and this has been attributed to an action on the capacity of platelets to take up 5HT, similar to that of reserpine but differing in some important respects (Marshall *et al.*, 12).

Such results of experimental research justifiably lead to the investigation of the blood platelet 5HT level in psychiatric illness. Feldstein *et al.* (6) have recently published data on the levels in normal subjects and schizophrenic patients. The results now to be described were largely collected in the course of clinical investigations of the effects of drugs and other physical methods of treatment in various diagnostic categories of patients; these are being reported separately.

METHODS AND MATERIALS

1. *5-Hydroxytryptamine Estimation.* The method of estimation of blood platelet 5HT is based on Brodie *et al.*'s (4) modification of the original spectrofluorimetric method of Udenfriend *et al.* (19).

The techniques of collecting blood, separating and counting the platelets

and adapting the 5HT estimation to the Locarte LMF/2 filter fluorimeter have been described in a previous paper (Marshall *et al.*, 12). In the earliest stages of this work duplicate estimations were not always possible; in the later stages, bloods were taken from patients on two or more occasions, each being estimated in duplicate. Since patients of all diagnostic categories and degrees of chronicity were studied randomly throughout a period of 18 months, no attempt has been made at weighting.

2. *Platelet Counts.* The method of estimation of 5HT requires the carrying out of a platelet count on the blood. It is therefore possible to express the platelet 5HT level in terms of nanograms, (ng.)/ml. of whole blood or of ng./10⁹ platelets (1 nanogram=10⁻³ μ g.). Hardisty and Stacey (11) have observed a fairly close correlation between the platelet count and the blood 5HT level. Since the spread of our normal values was less when calculated on a blood volume basis we have adopted this method throughout; however, details of the mean platelet counts for patient groups have been given in the results section. The normal range of values for platelet counts depends on the technique employed; using the method of Baar (1) we have observed that a range of 150-400,000 per c.mm. excludes only 5 per cent. of counts; these were all above 400,000.

3. *Subjects Studied.* These can be classified as follows:

(a) Normals. Twenty male medical, nursing, and laboratory staff, selected to give uniformity with respect to age (four per decade between 15 and 65).

(b) Patients receiving treatments of various types. They may be divided into the following groups:

- (i) Schizophrenics, acute.
- (ii) Schizophrenics, intermediate.
- (iii) Schizophrenics, chronic.
- (iv) Psychotic depressions.
- (v) "Non-psychotics", neurotics, psychopaths, alcoholics.
- (vi) True organic psychoses.

None of the patients studied had received any antecedent therapy likely to affect 5HT level.

(c) Patients suffering from post-encephalitic Parkinsonism were examined with the co-operation of Dr. I. M. Ingram, Psychiatric Unit, Stobhill General Hospital. Reserpine is well known to produce Parkinsonian side-effects and a complete disappearance of blood platelet 5HT, and it was desired to test whether these two facts were causally related. As transportation delayed the processing of these samples for 4-5 hours after withdrawal, control bloods were supplied, taken from depressive patients.

RESULTS

1. *Introduction.* On preliminary analysis of the data, differences between group means were observed which appeared to be significant. The most positive example was that of the three groups of schizophrenics for which the data are given in Table I; there was a highly significant difference between the blood platelet 5HT level for the chronic, older, patients and the younger groups. There was also a suggestion of a similar difference between the older (Crichton) and younger (Stobhill) depressive groups.

TABLE I
Description and Mean Blood Platelet 5-Hydroxytryptamine of
Groups of Schizophrenics

Group	Number	Mean Age	Mean Period of Hospitalization	Mean Blood Platelet Count	Mean Blood 5-HT Content and S.E.M.	
Acute ..	10*	25	2 weeks	249,000	197 ± 21	The difference between the mean levels of the acute and intermediate groups was not significant ($P=0.25$) but the difference between the means of these two groups combined and the chronic group was highly significant ($P<0.001$)
Intermediate ..	12	31	4 years	258,000	238 ± 24	
Chronic ..	7	47	16 years	277,000	387 ± 63	

* Included 3 females.

It was therefore decided (a) to add to the normal data in such a way as to provide a wide age range, and to do this also with the patient groups as far as possible; and (b) to submit all groups of data to a statistical analysis of the regression of platelet 5HT level on age.

2. *Normal Subjects.* The mean value for 20 male subjects of mean age 40.6 years was 196 ± 54 (S.D.) ng. 5HT/ml. blood. The mean platelet count was 307,000 per c.mm., the values for the two oldest subjects being over 400,000. The regression of platelet 5HT on age was

$$5HT \text{ (ng./ml.)} = 196 - 0.15 (x - 40.6)$$

The slope of the regression was not significantly different from zero ($0.9 > P > 0.8$) and it therefore appears that age has had no effect on platelet 5HT in this group.

The calculated 5 per cent. fiducial limits are 84–307, while the actual values ranged from 125 to 289. The ratio of the highest to lowest (2.3) is less than the ratio (3.3) observed when the 5HT is calculated on a per platelet basis.

An auxiliary study, carried out by Mr. G. Thom, has confirmed the observation of Pohle (17) that the platelet count in normal females is extremely variable at the onset of menstruation; it rose by as much as 60 per cent. (average 30 per cent.) in 48 hours following a drop which was, in many cases, equally rapid. In one normal subject, from whom blood was drawn every two days over the period of menstruation, the blood 5HT content was found to parallel the platelet count closely. It was therefore decided to omit all females from the statistical analysis.

3. *Crichton Male Patients.* The total number studied was 66. Their mean age was 39.5 years and platelet count 274,000 per c.mm. The blood platelet 5HT level, 255 ng./ml. was significantly higher than normal ($P < 0.05$). The regression of blood 5HT on age was given by.

$$5HT \text{ (ng./ml.)} = 255 + 1.18 (x - 39.5)$$

The slope of the line was not significantly different from zero ($0.3 > P > 0.2$).

4. *Schizophrenics.* Following the omission of the females and the inclusion of additional males, the group as finally studied consisted of 32 patients of mean age 35.5 years and mean platelet count 258,000 per c.mm., with no values outside the normal range. The mean blood platelet 5HT level was 250 ng./ml., which was just not significantly different from the normal mean level ($0.1 > P > 0.05$). The equation for the regression of blood 5HT on age was

$$5HT \text{ (ng./ml.)} = 250 + 2.22 (x - 35.5)$$

but the slope was not significantly different from zero ($0.2 > P > 0.1$).

The group has been subdivided in accordance with a series of clinical parameters. The blood 5HT levels for this series of subgroups are as follows:

Grouping		Mean Blood 5HT	Significance of Difference
A	One year or less since first admission ..	204 (14)	.1>P>.05
	Over one year since first admission ..	286 (18)	
B	One year or less since first symptoms ..	176 (8)	P=.05
	Over one year since first symptoms ..	275 (24)	
C	Clinical symptomatology Acute ..	201 (11)	.05>P>.02
	on date of test Static ..	284 (19)	
D	Diagnosis—process, nuclear schizophrenia	218 (24)	.4>P>.3
	Diagnosis—other types	267 (7)	

(The figures of A and B are based on all 32 cases, those of C on 30 cases, two classified as remitting being discarded; the figures for D omit one case classified as dubious.)

There is, perhaps, a factor, relating to length of hospitalization (A) or duration of illness (B), clinical activity of symptoms (C), or age (regression equation) which causes the statistical analysis of the data for the schizophrenics to approach and sometimes reach the standard criterion of significance. The common element in these measures—if there is one—seems to be temporal in nature.

There is no significant difference between the diagnostic categories (D).

5. *Psychotic Depressions.* This group numbered 16 males of mean age 51.4 years and mean platelet count 273,000 per c.mm., with all values lying in the normal range. The mean blood platelet 5HT level, 242 ng./ml., was significantly different from the normal mean ($P<.05$). The equation for the regression of blood platelet 5HT level on age was

$$5HT\text{ (ng./ml.)}=242+1.10\text{ (x-51.4)}$$

The slope is not significantly different from zero ($.5>P>.4$).

All cases were diagnosed as endogenous depressions. The platelet 5HT levels were remarkably uniform, the statistical variance being only one-quarter that of each of the other Crichton patient groups (schizophrenics and “non-psychotics”).

Some subdivision of the group along clinical lines was attempted. The mean 5HT level for 7 cases of mean age 57 years having a highly typical endogenous depression was 275 ng./ml.; that for 9 cases of mean age 47 years, in which symptoms additional to those of endogenous depression were noted, was 216 ng./ml.; that the difference approaches significance ($P=.1$), is due to the low variance rather than to its own magnitude.

Subdivision in terms of responsiveness to E.C.T. gave a similar picture, 8 cases of mean age 60 years with a wholly satisfactory response having a mean level of 260 ng./ml., while 7 cases of mean age 43 years in whom the response was less certain had a mean level of 222 ng./ml.; the difference is not significant ($P=.3$).

6. *“Non-Psychotic Patients.”* This group consisted of 17 neurotic, psychopathic, or alcoholic patients of mean age 36.3 years and platelet count 307,000 per c.mm., with two values 466,000 and 579,000. The mean blood platelet

5HT level, 276 ng./ml., was significantly different from the normal mean ($P < .05$). The regression of 5HT on age was

$$5HT \text{ (ng./ml.)} = 276 + 0.97 (x - 36.3)$$

The slope was not significantly different from zero ($P = .8$).

The group is much more heterogeneous than the two already considered and, in respect of two psychiatric parameters, there are differences between subgroup means.

Eleven patients, of mean age 34 years, had overt symptoms of anxiety at the date of the test, and had a mean 5HT level of 230 ng./ml.; six, of mean age 40 years, who did not show anxiety had a mean 5HT level of 360 ng./ml.; this difference is on the borderline of significance ($P = .05$).

A group of nine patients of mean age 38 years (six psychopaths, one obsessional neurosis with epilepsy, one high-grade mental defective, and a hysteric with epilepsy) had illnesses which might conceivably be related to ill-defined organic disturbance of cerebral function and these had a mean 5HT level of 313 ng./ml. The illnesses of the remaining eight (five with anxiety hysteria and three alcoholic) seemed obviously reactive to environmental provocation and showed no evidence—for example, electroencephalographic—of quasi-organic disturbance; this group, of mean age 35 years, had a mean 5HT level of 234 ng./ml. Although the difference appears large it is not significant ($.3 > P > .2$).

7. *Post-Encephalitic Parkinsonism.* Blood from twelve patients of mean age 54 years was received, together with ten bloods as controls from depressives of mean age 40 years. The average periods of hospitalization and illness were, for the encephalitics, 10+ years and 15+ years respectively and for the controls, 1 week and <6 months respectively. All encephalitic patients were receiving benzhexol hydrochloride.

The mean 5HT level for the controls, 158 ng./ml., was significantly lower than the mean level for the Crichton depressive patients ($P = .01$), (platelet count 262,000 per c.mm.). This suggests that transportation—by train—may have affected the level, but the groups were also not comparable in respect of age and perhaps in respect of other criteria for which full data were not available.

The mean 5HT level for the encephalitics was 259 ng./ml. (platelet count 280,000 per c.mm.); this is almost significantly higher than that for the control group ($P = .1$). However, one individual had a 5HT level of 735 ng./ml. and a platelet count of 535,000 per c.mm. The mean values, omitting this patient, were 216 ng./ml. and 257,000 per c.mm. but, owing to the reduction of the variance, P did not alter.

The considerable difference between the encephalitic and control groups in respect of length of hospitalization and illness may account for some of the difference in 5HT level, which, though not significant, would otherwise be disconcertingly great. The possibility of an action of benzhexol hydrochloride on blood 5HT levels cannot be discounted.

8. *Miscellaneous.* The Crichton male patient group was completed by one case of G.P.I., which was normal in regard to 5HT.

A number of cases of Huntington's Chorea were studied to see whether this genetically determined, presumably metabolic, disorder exhibited an abnormality of 5HT metabolism. We are indebted to Dr. J. R. Roy, Southern

General Hospital, Glasgow for this suggestion and for blood from some of his cases. The values, however, showed no particular trend.

DISCUSSION

In a previous paper (Marshall *et al.*, 12), in which the method of estimation of blood platelet 5HT was described in greater detail, evidence was presented to support the adequacy of the method in comparison with the more specific bio-assay and spectrophotofluorimetric procedures. Fluorimetric methods apparently give slightly higher values than bio-assay ones (cf. Hardisty and Stacey, 10) though no parallel studies appear to have been reported. The filter fluorimeter used in our study gives a value for normal subjects, 196 ± 54 (S.D.) ng./ml., almost identical with that obtained by Feldstein *et al.* (6) using a spectrophotofluorimeter, viz., 190 ± 80 (S.D.) ng./ml. for a group of 15 subjects.

The mean value for as representative as possible a group of 94 general hospital patients was found by Weiner and Udenfriend (20) to be 240 ng./ml., using a spectrophotofluorimeter. It seems possible that the mean levels of hospital patients, general and mental, are significantly different from the norm.

Feldstein *et al.* (6) have referred specifically to the occasional case with a very high urinary excretion of 5-hydroxyindoleacetic acid (the breakdown product of 5HT), and have emphasized the extent to which it affects statistical calculations. We have had a similar experience in respect of blood platelet 5HT. We have found nine values above 400 ng./ml. in 108 subjects (including the two groups from Stobhill) distributed as follows:

Normals	..	..	..	..	0/20	0 per cent.
Schizophrenics	..	..	..	..	3/32	9 per cent.
Psychotic depressions	..	..	..	..	1/26	4 per cent.
"Non-psychotics"	..	..	..	..	4/17	24 per cent.
Post-encephalitics	..	..	..	..	1/12	8 per cent.

Review of these individual cases in respect of both psychiatric and general medical history and current clinical status does not offer any explanation. We incline to the view that it would be necessary to investigate closely possible organic and dietary abnormalities in these cases before concluding that these individual levels are in any way related to mental illness. As a corollary, we doubt whether minor abnormalities in 5HT levels in patient groups can usefully be further investigated until the cause of these high values is found, and until something more is known of the physiological functions of 5HT outside the central nervous system and the factors which can influence its level.

The investigation of Feldstein *et al.* (6) was primarily directed to testing whether the blood platelet 5HT levels of schizophrenic patients were significantly abnormal, as might be expected on the basis of the theories adumbrated by Woolley (21) and Gaddum (7). The sizes of the groups of normals and acute and chronic schizophrenics approximate to those of the present study. Their findings in respect of schizophrenics resemble those reported here to the extent that the mean for the acute group is significantly lower than that for the chronic group. However, their figures are 120 and 170 ng./ml., respectively, compared with ours of 190 and 280 ng./ml. Since the normal means are essentially the same, their conclusion, that the blood 5HT level of the acute group is significantly low while that of the chronic group is normal, disagrees with our conclusion that the level in the acute group is normal while that in the chronic group is significantly high.

Such significance as these findings possess in relation to the theories of Woolley and Gaddum is reduced by the fact that the 5HT levels of the depressive and "non-psychotic" groups differ more from the norm than does that of the schizophrenic group.

SUMMARY

The results of a study of blood platelet 5-hydroxytryptamine (5HT) levels in 20 normal controls and 88 psychiatric patients are reported.

5HT levels in the controls are comparable to those of other studies. The levels in three groups of patients—schizophrenics, psychotic depressions, and a non-psychotic group—were higher than normal, to a statistically significant degree in the latter two. There was some indication of a temporal factor related to duration of illness, length of hospitalization or degree of chronicity, tending to raise 5HT levels in schizophrenia but no statistically significant regression with age itself was observed.

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TREATMENT OF SEVERE DEPRESSION BY IMIPRAMINE (TOFRANIL)

AN INVESTIGATION OF 100 CASES

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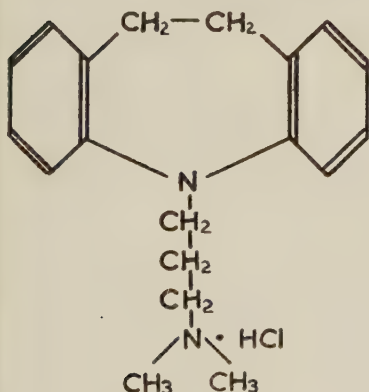
St. Mary's Hospital, Paddington, W.2

Ashford Hospital, Middlesex

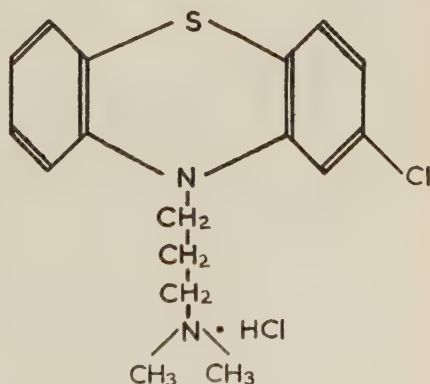
THE depressive syndrome is very distressing and incapacitating for any patient who suffers from it, and wherever it occurs psychiatrists are faced with a serious problem more particularly because of the consequent risk of suicide. The incidence of depressive illnesses has in my experience certainly not decreased during recent years, on the contrary it has probably increased and there is still an urgent need for more effective therapy to counteract the dire suffering and suicidal rate involved.

PSYCHOPHARMACOLOGY

This word is assuming increasing significance and importance for the clinical psychiatrist. During the last 10 years twenty-eight different chemicals (each with a proprietary name of its own) with tranquillizing and sedative effects on the nervous system, and five with stimulant ones have been introduced into the pharmacological field. None of these had a specific anti-depressant effect until the advent of imipramine (an amino-di-benzyl derivative, see Fig. 1)



Imipramine



Chlorpromazine

FIG. 1

a few years ago (Lehmann, 1958). This drug originated in Switzerland where the preliminary pharmacological and clinical investigations were made. Kuhn (1957) published the first paper on its clinical effects and since then other papers have appeared in Canada, the U.S.A., and Italy. The drug has only recently

become available in this country and this article describes a clinical investigation of its potentialities.

The discovery of convulsive therapy presented to psychiatry the first efficacious method of treating the depressive illnesses and up to date it has held almost a monopoly in successful results. The use of drugs in the treatment of depression other than neurotic depression has, in my opinion, been disappointing and seldom fundamentally successful, and this opinion is shared by probably the majority of clinical psychiatrists (see Kuhn, 1958, etc.). Amphetamine and Dexedrine stimulate cortical activity without counteracting the basic depressive processes and are drugs of addiction. Drinamyl (a combination of amphetamine and sodium amytal) is not radically effective, nor are pipradrol (Meratran) and methyl phenedyl acetate (Ritalin), chlorpromazine (Largactil) and the other phenothiazine derivatives (Stelazine and Fentazin, etc.) are almost useless except in schizophrenic depression. Reserpine (Serpasil) may aggravate depression and is strongly contra-indicated in its treatment.

Despite the efficacy of E.C.T. in most cases of depression it has certain disadvantages which have spurred on the search for a psychopharmacological agent, viz.: (1) the elaborate technique involved and well-known dangers such as laryngeal spasm when Pentothal is used in the "modified" procedure, (2) such complications as memory defect and a sense of fear for the treatment, (3) the difficulties of arranging maintenance E.C.T., (4) certain patients are physically unfit for this form of treatment.

There is a general consensus of opinion amongst psychiatrists abroad who have published papers on imipramine that this drug counteracts and dispels depression in a different and more potent manner than any drug manufactured hitherto. The present work was undertaken largely with the objective of confirming or refuting their claims.

CLINICAL INVESTIGATION OF IMIPRAMINE (TOFRANIL)

In effecting a clinical investigation of any drug one endeavours to reach conclusions regarding (1) its clinical effects and the indication for its use, (2) the optimum dosage and method of medication, and (3) its side-effects and their management.

The diagnosis of depression in the psychiatric sense is based on a syndrome of symptoms of which the all-important ones are:

1. The subjective feeling of depression itself with its concomitant feelings of sadness, despondency, hopelessness, and misery.
2. Negative thinking.
3. Lack of mental energy and initiative and feelings of fatigue.
4. Anorexia and insomnia.

This constant picture is varied by the presence or absence of both or either:

- (a) Ideas or delusions of guilt and unworthiness.
- (b) Mental agitation.

The classification of depressive illnesses still varies greatly from one author to another (see references). I have divided the present series of cases into the following categories:

(a) *Manic Depressive*. Patients qualify for this group by virtue of a cyclothymic extroverted temperament and personality, previous typical attacks, a family history of this illness, etc.

(b) *Endogenous*. Cases suffering from their first attack and whose personality traits and previous history did not qualify them definitely for the manic depressive group. In these cases an obvious physical or mental precipitating factor was present and they were subgrouped accordingly as puerperal, menopausal, post-hysterectomy, post-influenzal and endogenous-reactive (i.e. a mental reactive factor).

(c) *Senile Arteriosclerotic*. In these patients a depressive syndrome occurred for the first time in senile patients with arteriosclerosis and some degree of dementia. Senile patients without obvious dementia and arteriosclerosis were placed in the manic depressive or endogenous group.

(d) *Psychoneurotic*. The depressive syndrome occurring in patients definitely suffering from a psychoneurosis.

(e) *Psychopathic*. A depressive syndrome occurring in a psychopathic personality.

(f) *Schizo-affective*. Depression occurring in the group of psychotic patients who occupy a borderline between a schizophrenic and manic depressive state.

The use of rating scales is of dubious validity in presenting results. Straker (1959) considers them unwieldy and prone to add confusion to the results offered. I believe that the syndrome of depressive symptoms described above is an interdependent entity and that the symptoms improve or deteriorate together and not in measurably differing degrees.

Tuteur (1956) has called attention to the pitfalls and limitations of the "blind" and "double-blind" techniques of control involving the use of placebos and neither technique was used in this investigation. However, certain controls were implicit (see below).

Paul Hoch (1958) has stated: "Regardless of the methods you use today in psychiatry to observe behaviour changes, the only method which can be used, despite its many shortcomings, is the clinical one. Any attempt to replace it in the present state of our knowledge by all kinds of so-called scientific constructs is doomed to failure."

This is a clinical investigation and the results are graded on clinical criteria as follows:

1. *Recovery*. A recovery from the depressive syndrome of symptoms (including agitation and ideas and delusions of guilt and unworthiness) and from the debility associated with them. A return to pre-depressive activity and work.
2. *Much Improvement*. The distress and debility resulting from the depressive syndrome is greatly reduced and the patient is able to live at home or in an open ward of the hospital to perform useful work despite the persistence of depressive symptoms in mild intensity.
3. *Improved*. An improvement in depressive symptoms and although the depression is still present and so debilitating that the patients have to remain under constant nursing supervision.
4. *Unchanged*. No appreciable change in the depressive symptoms.
5. *Worse*. A deterioration in depressive symptoms due directly to the drug, or the development of mental side-effects necessitating withdrawal of the drug.

MATERIAL AND METHOD

The hundred patients involved in this investigation were all women, and all in-patients in St. Bernard's Hospital. Details of their age groups, etc., are shown in Table I.

TABLE I
Details of Case Material

Age Groups					Duration of Depression Before Treatment by Tofranil			
Under 20	..	..	..	1	Less than one month	..	..	6
21-30	..	..	..	9	1- 2 months	..	..	10
31-40	..	..	..	14	2- 3 months	..	..	12
41-50	..	..	..	20	3- 4 months	..	..	9
51-60	..	..	..	23	4- 5 months	..	..	8
61-70	..	..	..	20	5- 6 months	..	..	5
71-80	..	..	..	11	6-12 months	..	..	12
81-90	..	..	..	1	1- 2 years	..	..	16
Over 90	..	..	..	1	2- 3 years	..	..	10
				100	3- 4 years	..	..	4
					4- 5 years	..	..	3
					5-10 years	..	..	3
					Over 10 years	..	..	2

4. Patients experiencing their first severe attack of depression and this being their first admission to a mental hospital were treated with imipramine (instead of E.C.T.) from the beginning.

The method of prescribing this drug has varied from one psychiatrist to another. Some advocate a rapid increase of dosage over a short period followed by a reduction within a short period. In all the present series of cases 25 mg. t.d.s. was prescribed in the first instance. This dose was sufficient to produce recovery in some cases. Once the patient ceased improving on this dose over a period of a few days the dose was increased to 50 mg. t.d.s. and those who did not recover on this and who tolerated the drug well were in turn increased to 75 mg. t.d.s. and where necessary 100 mg. t.d.s. The dose was never raised beyond this level. In no instance were injections used nor was the practice advocated by some writers of rapidly increasing the dosage during the first few weeks and then gradually reducing it ever resorted to.

No cases were included in the series who had been treated and followed up for less than three months and none have yet been treated and followed up for more than nine months. Once the maximum effect of the drug had been obtained maintenance doses were continued. I decided in view of the marked liability for a relapse in cases of this type to err on the side of caution and to continue with the optimum dose for at least eight weeks after its maximum effect. Thereafter the dose was very gradually reduced. In twelve particularly severe or recalcitrant cases it was deemed necessary to give a few E.C.T. treatments while continuing as usual with the imipramine (Tofranil). Collective details of the treatment are presented in Table II.

TABLE II
Details of Treatment
Number Who had Received E.C.T. Prior to Imipramine
Treatment

Maximum dose given:									
25 mg. t.d.s.	..	..	..	..	..	..	..	..	22
50 mg. t.d.s.	..	..	..	..	..	..	..	..	45
75 mg. t.d.s.	..	..	..	..	..	..	..	..	22
100 mg. t.d.s.	..	..	..	..	..	..	..	..	11

Duration of Treatment

6 weeks-2 months	..	..	..	..	..	..	..	..	23
2-3 months	..	..	..	..	..	..	..	..	37
3-4 months	..	..	..	..	..	..	..	..	27
Over 4 months	..	..	..	..	..	..	..	..	13

Number of Cases Receiving E.C.T. During Imipramine Treatment—12

No. of E.C.T.s Given							No. of Patients
2	..	..	..	..	..	..	2
3	..	..	..	..	..	..	3
4	..	..	..	..	..	..	2
5	..	..	..	..	..	..	5

Careful observation was kept on all cases for any side-effects from the drug. Blood pressure readings were made twice a day and routine blood counts taken.

The same occupational and recreational regime nursing care and psychiatrist's supervision were available to these patients as to patients treated

by E.C.T. or other methods. Everything possible was done to help all patients to cope with any social, marital, or other problems confronting them. Thus a broadly constant environment was afforded as a control for comparing results of imipramine (Tofranil) treatment with E.C.T. and other treatments.

RESULTS

(a) *Percentages.* The grading of results was made on the criteria already mentioned. Table III represents the total results obtained in each type of

TABLE III

Showing the Therapeutic Effect of Imipramine on 100 Cases of Depression

Type of Depression	Recovery	Much Improved	Improved	No Change	Worse	Totals
Manic-depressive ..	34	7	3	2	2	48
Endogenous ..	19	3	—	—	—	22
Arteriosclerotic ..	6	4	3	1	1	15
Psychoneurotic ..	—	3	2	4	1	10
Psychopathic ..	—	1	1	—	—	2
Schizo-affective ..	—	2	—	1	—	3
Totals ..	59%	20%	9%	8%	4%	100

depression and in the full 100 cases. Of the 22 endogenous cases, eight were menopausal, three puerperal, two post-hysterectomy, two post-influenzal, and seven endogenous-reactive cases.

All cases in the "recovery" group have gone home well and free from depression, and it is likely that some cases in the "much improved" group of the manic-depressive and particularly the endogenous types will before long also grade to "recovery".

The cases in the "improved" and "no change" categories had been depressed for many months or years and had a bad prognosis, apart from two cases whose treatment had to be terminated because of side-effects too soon to produce any appreciable change in their depression.

In the arteriosclerotic group the results of treatment are assessed entirely upon its effect on the depression present. Needless to say, the degree of dementia was unaffected.

The comparatively poor results obtained in the psychoneurotic group were, in my estimation, to be expected in view of many years' experience of the treatment of such cases with E.C.T. The fact that the emphasis in the origins of such depressions is on the psychopathological rather than the endogenous factor probably accounts for this. The cases who failed to respond at all had suffered from a chronic neurosis for several years of such intensity as to necessitate hospitalization during most of that time.

The "much improved" psychopath responded by disappearance of her depression but was not placed in the "recovery" group because of the probability of a relapse and because her other symptoms have prevented her discharge from hospital.

The results obtained in two (much improved) of the three schizo-affective patients were really remarkable. These cases had defied all other treatments (i.e. E.C.T., chlorpromazine, trifluoperazine, etc.), but on imipramine their condition steadily improved until they are now better than since admission to hospital, free from depression apart from occasional short bouts, going

home for weekends, and apparently, contrary to all previous expectations, going to be fit for discharge home in the near future (Case No. 10).

The results were also analysed from the four viewpoints mentioned above.

1. Eighteen patients were unsuitable for E.C.T., eight being physically unfit (one auricular fibrillation, one recent stroke, one retro-peritoneal sarcoma, and five hypertension (B.P. 240, 234, etc.)), two having had laryngeal spasms, one with difficult veins, two with severe memory defect, and four being afraid and refusing E.C.T. treatment. They had been in hospital for periods varying from a few months to a few years before imipramine treatment. The beneficial results obtained in this group were beyond any expectation (Table IV) and indicate that imipramine has a valuable place in the treatment of depressive cases unsuitable for E.C.T.

TABLE IV
Response of Cases Unfit for E.C.T. to Imipramine

Groups	Re- covery	Much Im- proved	Im- proved	No Change	Worse	Totals
Manic-depressive ..	7	0	0	0	0	7
Endogenous ..	3	1	0	0	0	4
Arteriosclerotic ..	3	2	2	0	0	7
Psychoneurotic ..	—	—	—	—	—	—
Psychopathic ..	—	—	—	—	—	—
Schizo-affective ..	—	—	—	—	—	—
Totals ..	13	3	2	0	0	18

2. Although the majority of depressive illnesses respond to E.C.T. in every hospital there are a number who fail to do so sufficiently for discharge and remain chronically hospitalized for an indefinite period. Of the 800 female patients under my supervision in St. Bernard's Hospital, 29 were found to be in this category. Seventeen of these patients had been in hospital for periods of several months but less than one year. Of the 12 who had been in for over a year, 2 had been in hospital for 2 years, 4 had been for 3 years, 1 for 4 years, 1 for 5 years, and 4 for 6 years.

The results of imipramine on these 29 cases as opposed to those of previous E.C.T., etc., are shown in Table V. They are impressive and show that in certain cases imipramine may produce better results than E.C.T. One case responded to a combination of imipramine and E.C.T. who had not done so to either alone. It was this result which encouraged us to use E.C.T. in cases in groups (3) and (4).

TABLE V
The Effect of Imipramine on Cases who had Failed to Recover on E.C.T.

Type	Re- covery	Effect of E.C.T.			Effect of Imipramine				Totals
		Much Im- proved	Im- proved	No Change	Re- covery	Much Im- proved	Im- proved	No Change	
Manic-depressive ..	—	1	6	6	5	3	3	2	13
Endogenous ..	—	2	4	—	6	—	—	—	6
Arteriosclerotic ..	—	—	—	2	—	—	1	1	2
Psychoneurotic ..	—	—	1	3	—	1	—	3	4
Psychopathic ..	—	—	—	1	—	—	1	—	1
Schizo-affective ..	—	—	1	2	—	2	—	1	3
Totals ..	0	3	12	14	11	6	5	7	29

3. Twenty-six cases of this series suffered from recurrent depressive states and were re-admitted during the period of this investigation. They were treated immediately by imipramine instead of by E.C.T. as they had been on previous admissions. Table VI shows the results obtained.

TABLE VI

Re-admissions Treated with E.C.T. on Previous Admissions now Treated with Imipramine

	Re- covery	Much Im- proved	Im- proved	No Change	Worse	Total
Manic-depressive ..	16	4	—	—	2	22
Endogenous ..	1	—	—	—	—	1
Arteriosclerotic ..	—	1	—	—	1	2
Psychoneurotic ..	—	—	1	—	—	1
Psychopathic ..	—	—	—	—	—	—
Schizo-affective ..	—	—	—	—	—	—
Totals ..	17	5	1	—	3	26

The three patients who are registered in the worse category were worse not because of worse depression but because they became so agitated and distressed that imipramine treatment had to be terminated within a few days.

The psychoneurotic case was a very chronic case and E.C.T. on the previous admission had also only produced "improvement". The arteriosclerotic case was aged 77 and again E.C.T. had previously produced no better result than imipramine on this occasion.

Of the four "much improved" cases one was a case chronically maladjusted to life and with a bad prognosis. E.C.T. given for her depression (as an out-patient) had also failed to dispel the depression completely. One case who had "recovered" on imipramine and was about to go home developed purpura and on withdrawal of the drug relapsed and then settled in the "much improved" grade.

Four cases with very severe and distressing depression responded so sluggishly to imipramine that E.C.T. was introduced. They all recovered after very few E.C.T.s—one had two treatments, two had three, and one had five.

These results point to imipramine being as effective as E.C.T. in many cases of recurrent depression although a few cases prove unsuitable because of severe side-effects and some require E.C.T. in combination with the drug in order to accelerate recovery.

4. Twenty-seven first admissions were treated with imipramine instead of E.C.T. as they would have been in ordinary circumstances. The results are presented in Table VII.

TABLE VII

First Admissions Treated with Imipramine

	Re- covery	Much Im- proved	Im- proved	No Change	Worse	Totals
Manic-depressive ..	5	1	—	—	—	6
Endogenous ..	10	1	—	—	—	11
Arteriosclerotic ..	3	1	—	—	—	4
Psychoneurotic ..	—	2	1	1	1	5
Psychopathic ..	—	1	—	—	—	1
Schizo-affective ..	—	—	—	—	—	—
Totals ..	18	6	1	1	1	27

It is probable that the manic-depressive case who is "much improved" will, in due course, recover, and the endogenous case in that grade did "recover" and went home but has recently shown some symptoms of relapse and is, therefore, graded as "much improved". The dose of imipramine has been raised again, and it is expected she will recover again. The psychopathic case "recovered" from her depression but because of other psychopathic symptoms remained in hospital and was, therefore, graded "much improved".

Seven of this group were given some E.C.T. during imipramine treatment. This was considered necessary because their distressing symptoms did not yield rapidly to the drug. One was a severe psychoneurotic, four endogenous cases, and two manic depressives. One had two treatments, one had three, two had four, and two had five. All recovered except the psychoneurotic who was "much improved".

The psychoneurotic case labelled "worse" developed hallucinosis and the drug had to be withdrawn.

The figures for this group reveal that imipramine alone was successful in the treatment of the majority of depressive cases on their first admission but that E.C.T. was required in combination in some very severe cases who did not respond rapidly to imipramine alone.

It is worthy of note that all cases graded as "recovery" were very gradually weaned off the drug over a period of several weeks and so far none of them has relapsed into depression although they have been out of hospital for periods varying from three to six months.

(b) *Individual Cases.* The true potentialities of this drug can only be fully appreciated by direct observation of its effects but are further illustrated by reports of individual cases. The following are a few brief case histories:

Case No. 1. Age 67. History of 10 years fluctuating but continuous depression. Admitted 17 April, 1958. Developed laryngeal spasm from E.C.T. after 11 E.C.T. treatments had produced no improvement. Imipramine (Tofranil) started in February, 1959, in 50 mg. t.d.s. doses produced a recovery now retained for 5 months.

Case No. 2. Age 68. Previous attack 1953, attempted suicide. Admitted 1 June, 1959, after being in bed one month at home. Auricular fibrillation and old T.B. prevented E.C.T. Good and rapid response to imipramine. Much improved within four weeks. Home, recovered, two weeks later. Is still free from depression—3 months.

Case No. 3. Age 27. Three children: 3 years, 2 years, and 1 year old. Never mentally her usual self since birth of last child. Admitted very depressed having attempted suicide with aspirins. Given E.C.T., hated it and refused more after 5th treatment. Slightly improved. Put on imipramine (Tofranil). Maximum dose 50 mg. t.d.s. Further improvement within a few days and then a rapid recovery. Home for last 4 months.

Case No. 4. Age 46. Admitted 8 January, 1959. Suffering from severe depression with pronounced paranoid symptoms (no previous attacks). Menopausal. E.C.T., Largactil and Amargyl all ineffective. Appeared recalcitrant. 3 April, 1959 put on imipramine 25 mg. t.d.s. Dramatic improvement within a few days. (Then became agitated but this soon abated on Sparine.) Recovery within five weeks treatment. Has remained home, well on maintenance doses four months.

Case No. 5. Age 43. Depressed in some degree for previous six years. Endogenous reactive type. Marital difficulties during that time. In-patient on two occasions in 1958. Given E.C.T., improved enough to go home. Never really well. Second time E.C.T. had to be terminated due to memory impairment. Veractil, Ritalin and Amargyl tried with little benefit. Re-admitted on 29 March, 1959. Very depressed. Given imipramine (Tofranil) daily. Improvement within few weeks leading to complete recovery from depression for first time for many years. Now stands up for herself and so relationships with husband have improved greatly. Home five months.

Case No. 6. Age 53. Many home worries. Manic depressive and menopausal. (Previous attack, 1953, when she attempted suicide by gas and aspirins.) Admitted very depressed following attempted suicide with Doriden. Steady, uneventful improvement on imipramine but dosage had to be raised to 100 mg. t.d.s. before recovery was attained. Home three months.

Case No. 7. Age 65. Manic depressive type. Numerous attacks of severe depression since the age of 48, and never really free from depression since then. On each admission improved with E.C.T. sufficiently to go home but always relapsed, usually with suicidal attempts. Present admission 20 March, 1959. Placed on imipramine. On 75 mg. t.d.s. recovered completely from her depression. Felt better than she had done for many years. Marvellous appetite, sleeping well. Home five months.

Case No. 8. Age 53. Menopausal depression of one year's duration, worse last two months. Admitted 5 May, 1959. (First admission.) Very depressed and agitated. On imipramine 50 mg., steady improvement. Developed diffuse rash which responded rapidly to Periten (anti-histaminic). Recovery within a few weeks. Home for last three months.

Case No. 9. Age 30. Puerperal depression. T.B. during her adolescence, treated successfully now quiescent. Admitted 21 April, 1959. Depressed since birth of her first child three months previously. On admission was very depressed, suicidal inclinations. Insisted on departing four days later. Re-admitted 6 May, 1959. Condition unchanged. On imipramine gradually, improved and eventually recovered on 50 mg. t.d.s. Has been home very well for three months.

Case No. 10. Admitted 23 November, 1956, following attempted suicide, then aged 26. Schizo-affective psychosis. E.C.T. 60 treatments, a full course of chlorpromazine (Largactil) treatment (Blair and Brady, 1958) and later of trifluoperazine (Stelazine) had produced no substantial and sustained improvement. If ever sufficiently well to risk week-end leave she always returned worse and potentially suicidal.

In April, 1959, placed on imipramine. Little change to begin with but definite improvement as dose was raised to 75 mg. t.d.s. and then to 100 mg. t.d.s. Is now much improved. In an open ward for the first time since admission. Has ground and town parole. Goes home for week-ends. Manages housework and cooking. No relapse on return. Will probably recover before long. Has been made a voluntary patient.

Many more cases of interest could be cited but space forbids and the above varied cases represent a typical series of successful results.

MODE OF ACTION

The mode in which the improvement took place is interesting, and can be summed up thus: the symptoms and qualitative feelings of the depressive syndrome gradually diminished and disappeared as an entity and not separately and were replaced by those of well-being and vitality which the patient experienced as her usual self. Patients did not experience feelings of euphoria.

Each patient seemed to react to a specific dosage and there was no obvious reason why some reacted on only 25 mg. t.d.s. and others required 100 mg. t.d.s. In some cases improvement was rapid and dramatic, in others not commencing for a few weeks and then only gradual. In twelve cases suffering from severe symptoms response to imipramine was so slow that E.C.T. had to be given as well, which in every case produced marked rapid improvement within a few treatments. It may well be that the use of E.C.T. in combination with imipramine is going to be at least as important as it is in combination with chlorpromazine (in the treatment of schizophrenics).

In cases who presented an agitated depression frequently imipramine reduced the depression but not the agitation. The additional medication of Amargyl (chlorpromazine with amylobarbitone), or Sparine tablets almost invariably soon resolved the agitation.

Imipramine seems to be a powerful stimulant of appetite and all patients put on weight and on "recovery" looked very healthy and vivacious. (None of them put on grossly excessive weight and adiposity as some cases do on chlorpromazine.) Indeed the change of appearance and expression was one of the most remarkable effects of the drug.

Patients suffering from insomnia associated with manic-depressive or endogenous depression nearly all recovered from this symptom as the depression lifted and did not need any night sedative. In cases of a neurotic type or arteriosclerotic type night sedatives frequently remained necessary.

One case who had "recovered" within a few weeks on imipramine had to have the tablets stopped owing to developing purpuric spots. Her depression immediately relapsed considerably. Another who went home depression-free stopped taking her maintenance tablets because she felt so well. Within two days she was in deep depression again and had to be re-admitted as an in-patient. Further imipramine produced recovery again and she is now at home on a maintenance dose.

It was found to be always essential to continue maintenance doses until the basic processes causing the depression have abated and patients must always be weaned gradually from the drug.

SIDE-EFFECTS

Table VIII indicates the severe side-effects which occurred and their frequency. Apart from the major symptoms about to be described, atropine-like effects of a transient nature were common, e.g. nausea, disturbance of visual accommodation, headaches, and occasionally sweating. No case of photophobia occurred.

TABLE VIII

Side-Effects

Shakiness and agitation	..	..	..	..	..	..	..	..	9
Dizziness	..	..	..	..	..	..	..	..	7
Dryness of the mouth	..	..	..	..	..	..	..	..	16
Severe constipation	..	..	..	..	..	..	..	..	3
Erythematous rash	..	..	..	..	..	..	..	..	3
Epileptic fits	..	..	..	..	..	..	..	..	3
Purpuric patches on skin	..	..	..	..	..	..	..	..	2
Hypomania	..	..	..	..	..	..	..	..	2
Auditory hallucinations	..	..	..	..	..	..	..	..	1
Agranulocytosis	..	..	..	..	..	..	..	..	1

Shakiness and agitation were present in many cases in a mild and transient degree but then cleared up without any special medication. In the nine severe cases special medicative counteraction was required. In three cases the agitation was so bad that imipramine had to be abandoned altogether. The other six responded well and rapidly to Amargyl or Sparine tablets and the imipramine was continued in full doses.

Dizziness occurred in seven cases but this symptom was not connected with any marked decrease in blood pressure. The symptom cleared up spontaneously (probably as the result of an increased tolerance of the drug except in one case whose treatment had to be terminated). Amargyl, or Sparine, over a temporary period will often reduce and disperse this symptom.

Dryness of the mouth occurred in the early stages of treatment in many cases but in only 16 was it severe. In all cases it wore off within the course of several days and it presented no major problem.

Constipation in a mild degree was quite a common complaint but pre-occupation with bowel function is, of course, one of the characteristics of depressive illnesses. It responded to routine aperients except in three cases in whom it was severe and temporarily required enemas. If the depression increased and disappeared the constipation did as well.

An erythematous urticarial rash occurred in three cases and in each of them was soon abolished by Periten tablets (anti-histaminic).

Imipramine is closely related to chlorpromazine in its chemical structure (see Fig. 1) and it seems that like chlorpromazine it is epileptogenic to certain patients. Three patients (all elderly and with arteriosclerosis) had epileptic fits while on the drug—two had grand mals and one petit mals. However, in each of the grand mals cases only one fit occurred and in the petit mals only four sporadic fits.

Two cases developed purpuric spots. Blood counts and platelet counts were found to be normal in each case. They were thoroughly investigated by our visiting consultant physician. A diagnosis of purpura simplex was made in each case but this could not be definitely attributed to imipramine since one aged 72 was also on Doriden tablets for insomnia and the other, a chronic and resistive case, was also on Amargyl to counteract her agitation. Both cases recovered from their purpura on withdrawing all these drugs. Although it is not certain that the purpura was directly due to the imipramine these cases are included in the complications to draw attention to such a possibility.

Two manic-depressive cases whose depression was dispelled by imipramine veered into a mild hypomania. Imipramine was stopped and the hypomania soon disappeared and the patients "recovered".

One case of neurosis with depression treated by Imipramine recently developed auditory hallucinations. It seems probable that the drug was responsible for this symptom since the hallucinations (which had been very vivid) cleared up when the drug was withdrawn.

Blood pressure recordings were made every day. In some patients both the systolic and diastolic pressures varied very little throughout treatment. In others variations of 10 to 20 mm. Hg up or down occurred from day to day and in the large group of patients with a usual pressure of around 120/80 the systolic pressure sometimes dipped to the 90's or even 80's but the pulse pressure never dropped below 30 mm. In cases with hypertension imipramine almost invariably reduced the blood pressure substantially and retained the reduction while treatment continued. No case of an acute hypotensive attack occurred. Instability of nervous regulation of blood pressure may have accounted for the feeling of dizziness experienced over a transitory period by certain patients when rising from a lying or sitting position. Changes in blood pressure were not correlated to the dose of the drug prescribed.

One case of agranulocytosis occurred. The patient, aged 57, a manic depressive, was admitted on 1 June 1959 (previous attack 15 years ago), and placed on imipramine which was gradually increased to 100 mg. t.d.s. On this her depression showed increasing improvement and had virtually recovered when, on 19 July, 1959, seven weeks after the commencement of treatment, she complained of a sore throat and developed a slight pyrexia. A blood count revealed agranulocytosis with a white cell count of 1,700. Next day the count was 1,500. The drug was, of course, withdrawn and a very rapid spontaneous recovery in the blood picture occurred. By 28 July, 1959 (i.e. eight days after commencement), the white count, which had increased each day, reached 8,000 with 69 per cent. neutrophils and 26 per cent. lymphocytes. This patient was also on Amargyl tablets for agitation, so it is not known whether the agranulocytosis was due to Tofranil alone or the combination.

No other significant change of blood count was found in any of the counts made either in the earlier or later stages of treatment. No definite eosinophilia occurred—possibly due to our scheme of gradual increase in dosage which I adopted.

In no case did even a suspicion of liver dysfunction occur.

Two cases of this series died during the investigation, one aged 72 from a severe haemorrhage from an old gastric ulcer, the other aged 96 from arteriosclerosis and cardiovascular degeneration. In neither case could the death be in any way attributed to imipramine.

As a matter of interest it is worth recording that one chronic neurotic patient determined to commit suicide did not swallow her tablets and having hoarded 44 of them took them all at once and informed us a few hours later. Her blood pressure sank to 90/60 and later to 85/50. She was treated by raising her bed and giving her repeated small doses of Digoxin. Her systolic blood pressure did not return to over 100 mm. for two days. However, apart from a feeling of weakness and light-headedness she did not complain of any particular distress or discomfort and recovered to her usual self uneventfully, except for an epileptic fit on the second night after the overdose.

Altogether in eight cases imipramine had to be terminated because of side-effects—three cases of extreme agitation and shakiness, one of severe dizziness, one of auditory hallucinosis, two of purpura, and one of agranulocytosis. It was not terminated in the cases who had epileptic fits.

DISCUSSION

In 1957 Kuhn in Switzerland published the first paper on the treatment of depressive states by an aminodibenzyl derivative, imipramine hydrochloride (Tofranil). This drug is closely related in chemical composition to chlorpromazine (see Fig. 1) but its properties were found to be very different. Contrary to chlorpromazine, which is practically useless in the treatment of depression, imipramine was found to have a specific effect in dispelling depression. The pharmacologic way in which this is effected is still unknown but it has been designated a "thymoleptic" (mood regulating) drug.

Despite the well-recognized difficulties in assessing the potentialities of therapeutic measures for depression owing to the liability for spontaneous remissions, the present investigations indicate the definite potent anti-depressant effects of imipramine, for the following reasons:

1. It has been effective in chronic cases of depression where all previous therapy has been ineffective.
2. In cases unsuitable for E.C.T. owing to serious physical illness, refusal to accept this form of treatment, very difficult veins, etc., it has frequently produced "recovery" and "much improvement".
3. A dramatic and rapid change following the introduction of imipramine occurred often enough to convince one that the change was due directly to the drug.
4. The results obtained from imipramine treatment on recent cases who would ordinarily have been treated by E.C.T. were at least as favourable as one could have anticipated from the latter treatment.
5. The convincing percentage results in the total material treated (Table III).
6. The subjective accounts of the patients successfully treated, especially those who had previously had E.C.T.

The present results substantiate those described by other writers (see references) who have all confirmed the marked anti-depressant effects of this drug. For instance, Lehmann *et al.* (1958) in 84 patients obtained the following results: Recovered 18 (21 per cent.), Much Improved 33 (40 per cent.), Improved 19 (23 per cent.), No Change 13 (15 per cent.), Worse 1 (1 per cent.);

Azima (1959) in 100 cases obtained marked improvement in 44 per cent. and moderate improvement in 38 per cent. Mann and MacPherson (1959) in 70 cases obtained "recovery" in 28.5 per cent., "much improvement" in 34.2 per cent., and "improvement" in 18.5 per cent.; and Fabio *et al.* in 50 cases recorded a "clinical remission" in 32 per cent. and "appreciable improvement" in 42 per cent. The individual case histories published by them are not less remarkable than those in this article. My results agree with those who have obtained the best results in the manic depressive and endogenous types. I have found that doses of 75 mg. and 150 mg. per day are effective (with patience) in most cases and that doses above 300 mg. per day are seldom necessary and this again is in agreement with observations by Kuhn (1958), Azima (1959) and Mann and MacPherson (1959), although Lehmann *et al.* (1958) and Sloane *et al.* (1959) used as much as 600 mg. per day in a few cases.

My findings regarding the general clinical mode of action of this drug on the depressive syndrome are in keeping with those described by Kuhn (1958) and it is not appropriate in this article to discuss its pharmacological mode of action. Fazio *et al.* (1958) reports the success of combined imipramine and E.C.T. therapies when neither has succeeded alone in two cases. Lehmann *et al.* (1958) refers to the necessity for using E.C.T. in combination with imipramine in severe cases where rapid result is required. In the present series 12 cases have required combined E.C.T. for this purpose.

Like chlorpromazine, imipramine has many side-effects. In the present series no seriously adverse side-effects occurred other than one case of agranulocytosis which rapidly recovered spontaneously. No previous case of agranulocytosis due to imipramine has been described, but this case had also been having Amargyl. It is not certain whether the two cases of purpura simplex were directly due to the drug. So far none of the authors of other articles has found any of them to be of any serious consequence, but Kuhn (1958) reported two transient cases of jaundice, and Lehmann *et al.* (1958) one case of myocardial infarction which might have been due to the drug. Lehmann had two cases of epileptic seizures due to imipramine. Mann and MacPherson (1959) describe an initial dramatic fall of blood pressure of up to 100 mm. in a few cases and the development of auditory hallucinations and delusions in one case. They also refer to immediate intolerance in which the patient is completely overwhelmed by marked jerkiness, dizziness, palpitations, tension, and agitation. The two severely agitated cases in my series were in this category. Lehmann (1958) found visual hallucinations as a complication in five cases. Steck *et al.* (1958) also had a similar case.

Side-effects are, of course, of the utmost import and insufficient cases have yet been reported to be certain whether any of them may be really dangerous. A gradual increase of dosage along the lines I have indicated will probably minimize the chances of serious complications but it would appear advisable, in the present stage of our knowledge, for patients wherever possible to be treated in hospital, and if they are treated as out-patients for them to be seen frequently at a clinic or by their practitioners.

It seems with reference to our up-to-date experience of imipramine we are in a stage similar to that of the early days of chlorpromazine treatment. Imipramine seems to be a potent anti-depressant drug with many side-effects, and further investigation is required before final conclusions are reached regarding its therapeutic potentialities, the best methods of counteracting its side-effects, and its place in the treatment of depression in relationship to E.C.T. and other anti-depressant drugs now appearing on the market (such as various

mono-amine oxidase inhibitors). A final assessment of the proportionate values of the various therapeutic measures for the treatment of depression will only be possible when further research has revealed the true aetiological changes occurring in this condition and the extent to which each therapeutic agent counteracts them. In the meantime it appears that imipramine (Tofranil) holds a place in the treatment of depression approximately equivalent to that held by chlorpromazine (Largactil) in the treatment of schizophrenia.

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A CLINICAL CONSIDERATION OF PSYCHOPATHIC PERSONALITIES*

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THE concept of psychopathic personality in this presentation stresses a disorder of personality development. In these patients one finds a poorly organized personality with contradictory strivings, lacking consistency and unity in experiencing and acting. Disturbances of organization may be noticed in any phase of personality development but for various reasons they are most noticeable in adolescence and adult life. In this concept of personality organization and its disorders, psychologic, physiologic, and social aspects are considered but none of them is made the basic issue. The organization of the personality may be too loose or too rigid. In the too rigid organization, we find unbending persons with, or without, projection. In these persons certain personality features may be exaggerated and adaptation to the demands of life might be difficult. This discussion will be limited to the loosely organized personality with its features of immaturity, dependency and inadequacy, impulsiveness, aggressiveness, and inappropriate control of drives and desires.

The characteristics of the behaviour of the poorly organized personality is alike to that of the disorganized personality; i.e. the previously satisfactorily organized personality which becomes disorganized due to schizophrenic illness or cortical damage. Clinically, the differentiation between poor organization and disorganization of the personality is frequently possible only by the patient's life history. The occurrence of a disorganizing illness in a poorly organized person will be difficult to recognize in its early stages.

In a previous publication (1) I was able to demonstrate the changing psychopathologic picture in the same patient in a manic illness in adolescence, in the phases of maturing, and of mature personality. The same features as seen in the adolescent patient will appear in the poorly organized adult. They can be summarized in manic reactions as impulsiveness, poorly controlled emotional outbursts, aggressiveness, fear, far-reaching thinking disorders, social deterioration, and anal-erotic manifestations. In the depressive pictures, one notices sulkiness, marked sensitiveness to criticism combined with tactlessness, lack of emancipation as seen in homesickness, resentfulness, fear, confusion, unreality and familiarity experiences. It is obvious that in dealing with such manic and depressed patients the psychiatrist has to modify his psychotherapeutic approach and adjust his expectancy with regard to social adjustment while under treatment.

In recent years we had an opportunity to study in several poorly organized personalities as well as in schizophrenic disorders an acute psychopathologic episode which was characterized by intense sexual excitement, resentment and fear. In the most intense degree the patient experiences and demonstrates frank and frequently aggressive both hetero- and homosexual desires, expressed in

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talk and actions (including sexual advances to others, frank or ill-concealed masturbation and exhibitionism). Auditory hallucinations of sexual, threatening, or accusatory content are frequent as well as paranoid delusions. The acute phase may last from a day, to several days, to weeks, usually subsiding rapidly. The patients rarely have a clear memory of this episode but are able to discuss fragments. If one pushes aggressively in the therapeutic discussion, the excitement will be prolonged or worsened. When the physician discusses the content of the episode after it has subsided, there is a distinct danger of the sexual excitement recurring and frequently lasting for many weeks. Recurrent episodes are more difficult to deal with because the patient shows more aggressiveness and combativeness than previously. The excitements react well to interruption by electric convulsive treatment or by chlorpromazine. (This drug seems to react especially well on moderate and marked sexual excitement, resentment, and hostility.) These sexual excitements seem to occur frequently in poorly organized, that is psychopathic, personalities, especially when they have poorly repressed homosexual desires. In these patients the prognosis seems to be fair while it is good if these reactions occur in well-organized personalities with chronic psychoneurosis and an acute depression or manic excitement. Some of the cases of delirious mania (Bell's mania) belong to this group. In some of those patients no recurrence has taken place over a period of ten years or longer. In psychopathic personalities and in the still poorly organized adolescent, repeated reactions seem to be more frequent, occasionally terminating in chronic disorders. It is difficult to say whether the original episode was the beginning of a schizophrenic episode or whether psychologic and physiologic factors may have led to a permanent disorganization.

It might be appropriate to mention that in the last year we have found interesting biochemical changes in the blood serum of some of these patients. In the acute phase, there seems to appear an increase of a bradykinine-like substance in the serum of the blood. While the normal amount of bradykinine seems to be between .5 and 1.5 gamma in 1 c.c. of blood, in these patients we found 2 to 10 gamma.

In psychopathic personalities the sexual excitement, which is usually well defined in onset and ending, may take on the character of certain chronicity. It is frequently difficult to distinguish the lack of sufficient self control in psychopathic personalities from the inability to control intense sexual desires. A fourteen-year-old girl was admitted to the Clinic because her family had found out that during the past year she had intercourse with several men ten years her senior. The patient was from the beginning difficult because she showed readily poorly controlled anger reactions, was rude to the personnel and was soon rejected by the patients. She became flirtatious with the male patients and after four weeks developed a sexual excitement, in which she exposed herself, kissed the men, shouted for intercourse, and at the same time she was anxious and appeared unhappy. The excitement was well controlled with chlorpromazine, but when the drug was discontinued, she remained easily angered and used flirtatious and sexual advances to receive attention from older adolescents. It became obvious that the sexual drive, although more intense than average, was not the essential problem, but her unwillingness to control her emotions and desires in general and her inability to form stable relationships with other people.

The following case of a 28-year-old married woman suffering from a schizophrenic illness is interesting because the sexual excitement occurred several times in varying intensity and the final outcome after five months was complete

re-integration. During her seven years of marital life with a moody and markedly alcoholic professional man, the patient became increasingly resentful. In September, 1957 she felt sexually attracted to another man and became tense and tried to find relief in heavy drinking. In November, 1957 persons in her environment appeared to her like in a dream, and at the beginning of December she developed delusions that she was "part of a psycho-drama" and was Christ. Previously she had been in good health. Since adolescence she had been a lonely, quiet, but cheerful person. Her poor housekeeping caused much friction with her husband. Her attention and devotion was directed toward her five-year-old daughter. Her relationship to her father and mother, who were divorced when she was an infant, had never been close emotionally.

On admission, January, 1958, she was well groomed and apparently at ease, discussing her past delusions freely. There was no obvious thinking disorder. She felt "hopeful" that she might be helped but was not able to state for what. Two days later the other patients seemed to be personal acquaintances. She developed marked sexual unrest, recognized in exposing herself and flirtations with men and women. She became fearful and suspicious, shouting and at other times stuporous and posturing. Everything seemed like in a dream. She expressed the delusion that the physician was her husband and demanded intercourse. When he refused she became angry and fearful (she explained later that she became afraid because she could not understand his rejecting behaviour). At this phase of the excitement the blood plasma contained 2 gammas per c.c. of blood of a bradykinine-like substance. After five days her behaviour became quiet, but she continued to experience erotic sensations in her vagina. She recognized persons in her environment but expressed the delusion that her husband and child were dead. She appeared depressed and frequently cried. After four weeks she again experienced increased sexual desires directed to her absent husband, without fear or resentment. At this time there was no increase of the bradykinine-like substance in the plasma.

It may be difficult to understand such a sexual excitement without a description by the patient. In this patient, for instance, the sexual excitement was characterized by intense desire for intercourse and advances to the physician whom she believed to be her husband. When he did not respond, she felt intensely resentful and angry. During this phase the bradykinine-like substance was 2 gamma. She was studied at frequent intervals after her excitement had subsided and her bradykinine-like substance varied from .5 to 1 gamma. When the patient again showed a less-marked but well-defined sexual excitement in which she had marked desire for intercourse with her husband but recognized the physician as such and therefore did not respond with resentment, the bradykinine-like substance was not increased. Later when again sexual excitement was accompanied by resentment, there was an increase of the substance in the blood. I wish to stress that these observations were made on sexual excitements in schizophrenic disorders as well as psychopathic personalities, arguing for the possibility that far-reaching disturbances in the physiologic functioning may occur in both disorders.

In this connection it might be worth while to mention observations which have appeared in literature indicating that in severe behaviour disorders in young adolescents an abnormal electroencephalogram may become normal when the patient comes to maturity. In these patients, previously diagnosed psychopathic, such behaviour may gradually disappear. This is in contrast to adolescent psychopathic behaviour with normal electroencephalograms where the abnormal behaviour seems to persist into adult life. On the other hand,

there are psychopathic states with abnormal electroencephalograms where these pathologic abnormalities exist and where the patient does not show improvement. We obviously deal with various types of psychopathic states which need to be studied. In our own study of adolescents in the in-patient service, the prognosis has been especially poor in adolescents with explosive behaviour, marked hostility, and inability to form a close relationship to the physician or nurses. In these patients we frequently found an epileptic-like electroencephalogram. Several of these adolescents have remained in psychiatric hospitals for a period of 5 to 10 years and have deteriorated in behaviour but did not develop schizophrenic disorders. Their behaviour was little influenced by prolonged intensive psychotherapy, drug treatment, insulin and electroconvulsive treatment and, in one case, lobotomy.

There are some psychologic observations which deserve to be stressed. In the poorly organized psychopathic personality, one frequently deals less with acting-out in the true psychoanalytic sense than abreaction, that is, emotional catharsis. Frequently one may mistake for acting-out the patient's unwillingness to control his behaviour and exert suppression. This behaviour is an act of living-out impulses and different from the abreaction of intense emotions or from acting-out which involves a display of emotions related to previously repressed experiences.

Psychoneurotic symptoms often related to anxiety or resentment, occur frequently in psychopathic personality disorders. However, the important aspect of psychopathic difficulties is not neurotic acting-out, but the inability and unwillingness of the patient to control his behaviour. The resulting disturbances of social relations are considerable. In addition, these patients frequently show inadequacy in developing social values. Both the lack of suppression of emotional reactions and the inability to recognize social obligations, lead to asocial and antisocial behaviour. These tendencies result in considerable difficulties in the social adjustments in a hospital. On the open floors there is an inability to accept social obligations persistently. On the closed floors there is a rebelliousness to the restrictions. In our hospital where we have small groups, these patients do not present serious difficulties but they do disturb the social life of the group. If several such patients are grouped together, they either separate from the group or exert a disintegrating influence. They attract other inadequate personalities, for instance, schizophrenic patients, who, depending on their psychopathologic findings, will either become a follower or a leader of the group. These observations are similar to those made by Maxwell Jones in his study of a therapeutic community. Very interesting observations were made by Alexander H. Leighton (2, 3) in the county which he studied in Nova Scotia. He observed that such persons form a group which withdraws from the rest of the community. The effect of such groups on the community may not be very disturbing when the community succeeds in rejecting the group and keeping them outside their own borders. The same reactions may occur in a hospital where the psychopathic patient, especially in conjunction with others, may be rejected and, one might say, isolated by the constructive forces of the total group. In other groups where insecurities and instabilities are poorly controlled, these psychopathic patients can disturb the group which may disintegrate in a short time. It has been our experience that a healthy atmosphere can be established only if the group is reorganized by the transfer of the dependent and socially poorly adjusted individuals to another stronger group and by the addition of a well-organized personality to the group under discussion. In the Payne Whitney Clinic, where few psychopathic personalities

are admitted, but where we have many immature adolescents and disorganized schizophrenic patients, a sound balance is possible if these patients are mixed with well-organized persons who have developed depressions or psychoneurotic reactions which are not socially disturbing.

It is worth emphasizing that the shy, dependent, and inadequate schizophrenic patient is able to establish warm relations with other patients in the group. In contrast to the psychopathic personalities, they are not rejected. The difference between these two types of patients is insufficiently recognized by nurses and physicians and is rarely appreciated. It is also of interest to note that, in our experience, at the time of admission or shortly thereafter, the psychopathic personality seems to adjust well to the hospital rules and the other patients but begins to show social maladjustments after 2 or 3 weeks. Efforts at re-education in general, and especially social adjustment, seem to take a long period of time and our therapeutic results after a few months are frequently poor, especially in the aggressive type. They are somewhat better in the passive and adolescent patient. In schizophrenic patients who present similar behaviour disorders, however, the course in the hospital is different. After considerable initial social difficulties these patients prove to become amenable to persistent re-educational efforts and to learn from a careful psychologic and social analysis of each recurrent behaviour difficulty.

The lack of "vital", i.e., vitally important values, has been stressed by Klages as early as about 1920. In more recent years the same features have been considered of fundamental importance in existentialistic and phenomenological psychiatry. I happen to remember this early contribution of Klages especially well because Dr. Angus MacNiven and I, when we were at Johns Hopkins Hospital in 1925, discussed these aspects with considerable interest. At that time, Dr. MacNiven was puzzled by the use of the concept of insight in psychiatry and its application to psychotherapy. These remarks which I had difficulty in accepting fully at that time were appreciated much later in psychotherapeutic discussions and literature. What puzzled a young psychiatrist in 1925 has become a topic for serious discussion in the last 15 years.

The application of the changing attitude to achieving insight as an important therapeutic factor is well demonstrated in the treatment of psychopathic personalities. The therapeutic goal now consists of several equally important aspects among which insight is limited to the understanding of conscious behaviour. It is essential to determine the multitude of strivings which may be present simultaneously. The therapeutic task is to reorganize those which might work constructively. A related aspect is the analysis of the patient's successes in life which should result in the establishment of some degree of critical self-confidence. It may be difficult for a physician to recognize what might be considered successful episodes in the life of some psychopaths. To reach acceptable, positive social relations implies a willingness and an ability to adapt to changing as well as persistent disturbing or, at least, unsatisfactory conditions. The more specific goals in social adaptation depend to a large extent on the physician's personal life philosophy. In some patients a possible living with psychopathologic relapses outside the hospital and other institutions is the main goal. In others, a prolonged stay in the hospital with the willingness to become self-supporting as an obligation to the community may be the best solution. There again, the goal may be the ability to attain contentment in an environment to which the patient must adapt and to develop behaviour which is tolerable to others.

It is unclear what role the establishment of healthy identification plays

in good therapeutic results. In our treatment of adolescents we become aware of the value of identification by the same patient with his immediate therapist as well as with other physicians who had contact with him, with nurses, occupational therapists, and teachers. Identification may be in a very limited field and with the same therapist in several fields of human behaviour. It seems possible that the poorly-organized personality cannot establish the same kind of identification with his therapist as the psychoneurotic patient. In adolescents the results of identification are tenuous but very helpful in achieving a sound personality organization at maturity. In the psychopathic personality which seems incapable of reaching a fully-organized synthesis of its many strivings these past identifications may act like posts for guidance and transient safety.

The therapeutic possibilities in ambulatory therapy are much more limited in some respects and much wider in others. Psychotherapeutic re-education and environmental manipulation are the assets of a controlled social setting. The study of life situations is an asset of ambulatory treatment, and the physician will have to evaluate how much tolerance can be expected from the patient's social group. In addition to psychotherapy of the individual the aid of social workers is needed. A different problem is presented when a psychiatrist is called to advise with regard to the handling of problems in a psychopathic person who suffers from a physical illness, since such patients may present many difficulties in adaptation to their physical illness or to medical or surgical hospital.

SUMMARY

The psychopathologic concept of loose organization of the personality seems to have considerable validity for certain types of psychopathic personalities and to offer a basis for investigation and for selective and planned psychotherapy.

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THE EFFECT OF 1-ARYLCYCLOHEXYLAMINE (SERNYL) ON TWELVE NORMAL VOLUNTEERS

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THE production of "model psychoses" in animals and man by a variety of chemical substances is of great interest. While the relationship between disturbances so produced and schizophrenia are problematical, these investigations may eventually throw light upon the causes of this condition. More important, at present, is the fact that the investigation of the way these drugs modify various aspects of normal psychological functioning is of great value in suggesting the physiological and biochemical processes that underlie these functions.

Sernyl is a new drug which has recently been investigated because of its psychotomimetic properties which limited its use in anaesthetic practice where it was originally used.

REVIEW

The search for an efficient intravenous anaesthetic led to a series of cyclohexylamine derivatives being synthesized and studied in the laboratory. These compounds produce a blocking of sensory impulses so that surgical procedures can be carried out without concomitant sleep and without significant depression of respiration and circulation. The first of the series to be investigated was 1-arylcyclohexylamine (Sernyl). Pharmacological studies on experimental animals showed that Sernyl has a local anaesthetic action approximately equal to procaine. It has no adrenergic blocking, ganglionic blocking, anti-cholinergic or anti-histaminic action and it produces no significant changes in respiration or blood pressure at non-lethal dosages. Its chemical structure, with the related compound cyclohexamine, and also pethidine, is shown in Figure 1.

It was shown, by observations on experimental animals, that Sernyl was a potent non-toxic drug. When 10 mg./kg. was injected into monkeys, a profound state of analgesia resulted and operations were performed without additional anaesthesia.

It was noted that "during the operations the animal had its eyes opened and looked about unconcernedly". Sernyl was then investigated as an anaesthetic agent in 64 patients by Greifenstein *et al.* (1958). It was found that at a dosage of more than 0.5 mg./kg. the patients became agitated, and at 1 mg./kg. rigidity occurred, followed by catatonia and convulsions. A dosage of 0.25 mg./kg. was found to be satisfactory and, in 30 of the patients, Sernyl was used as the only anaesthetic agent for operations that ranged from simple biopsies to gastrectomies. In the other patients, muscle relaxants and nitrous oxide were

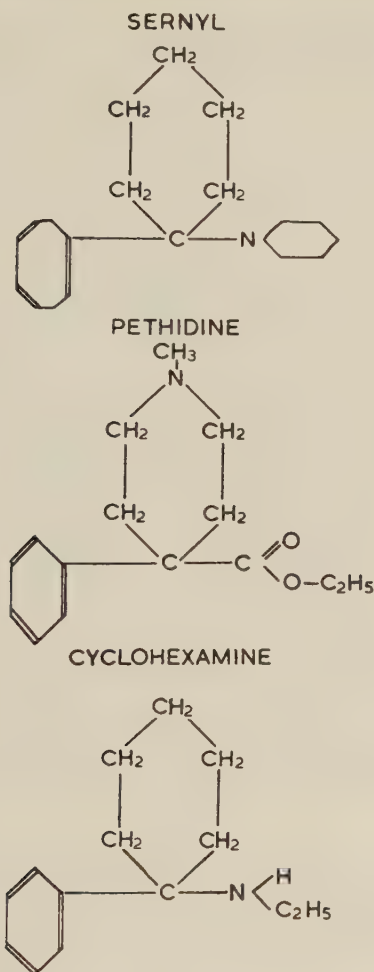


FIG. 1.—Chemical structure of Sernyl and related compounds.

- (a) Sernyl.
1-(phenylcyclohexyl) piperidine monohydrochloride.
- (b) Pethidine.
1 methyl 4 phenylpiperidine. 4 carboxylic acid ethylester.
- (c) Cyclohexamine.
N-ethyl-1-phenylcyclohexylamine monohydrochloride.

also used. It was noted that, once recovered, the patients had no recollection of any painful stimuli during the operation; only the initial venepuncture was remembered then nothing more until they "came to". Unfortunately 10 of the 64 patients presented very difficult nursing problems in the post-operative period. They showed severely agitated, bizarre behaviour while echolalia and logorrhoea were also noted. Because of these reactions, the use of this compound in anaesthesia was discontinued by these workers, though another related substance, cyclohexamine, has been studied (Lear *et al.*, 1959) but again post-operative disturbances of a psychological nature are common.

Sernyl was then investigated by a psychiatric team from Detroit (Luby *et al.*, 1959). Sernyl was given intravenously at a dose of 0.1 mg./kg. to nine

normal subjects and nine patients, four of whom were patients with chronic schizophrenic illnesses. In these schizophrenics, there was an intensification of the thought disorder and they became more difficult to manage. These behavioural changes continued for one month after the administration of the drug. The symptoms and signs produced by Sernyl in the normal subjects will be discussed later.

The sites of action of Sernyl are not known, though it is presumed to act selectively on the thalamus and mid-brain, producing impairment of pain, touch and proprioception. Meyer *et al.* (1959) reported further on the use of Sernyl as an anaesthetic agent and reported the electro-encephalographic changes seen after its administration. First there is a disappearance of alpha and beta activity, followed by a definite slowing, diffuse in nature but preponderant in the occipital, temporal and parietal regions.

Because of its action on the thalamus, Luby *et al.* (1959) have considered that Sernyl is an "interoceptive sensory blocking agent with psychotomimetic sequelae". They compared its action with results of exteroceptive sensory deprivation described by the McGill investigators (Bexton *et al.*, 1954) finding some similarities but "the disturbance in body image and the impairment in the symbolic process were far more severe with the drug than has been reported in any experiments during environmental sensory deprivation". These investigators also gave Sernyl to two patients under condition of sensory deprivation, finding that there was a greatly reduced verbal productivity, the experience being described as "sheer emptiness" as the volunteers were deprived of all external and internal stimuli.

With this background in mind, the aim of the present investigations was to study the effects of Sernyl from a psychiatric and psychological point of view on volunteers, then, from this pilot study, to suggest possible lines of investigation.

MATERIAL AND METHOD

Sernyl was given to 12 normal volunteers—8 trainee psychiatrists and 4 psychologists. The drug was given in a quiet room, the subject lying comfortably on a couch. The first 8 volunteers were given 0.1 mg./kg. body weight by injection over five minutes. Vomiting, however, occurred in two volunteers and so the dosage was lowered to 0.075 mg./kg. At this dosage, the effects were still easily observed; vomiting, however, occurred in two more subjects. The subjects were told that they were to receive a drug that produced some psychological disturbances but no detailed information was given. It was realized that the suggestibility of our volunteers, all working in the field of mental disorders, and the expectant atmosphere of the experimental situation, could produce symptoms and signs. However, as the investigation proceeded, we became aware of a common central theme to each Sernyl experience, which we were particularly interested in. The occurrence of certain different accessory symptoms—e.g. anxiety, suspiciousness—were probably mainly dependent on personality factors and have not been commented on. (One subject was given two injections on separate occasions, one of sodium amytal, the other of Sernyl, in a random order. Observations suggested that one could be in no doubt as to which drug was Sernyl and that suggestion played little part in producing the gross effects observed.) Psychological testing was carried out before the drug was given, following which, the subject was asked to describe his experience for the first 10–15 minutes, when the testing was repeated, as it was on two or three subsequent occasions. Answers to proverbs were recorded on tape and analysed by

an independent judge, using standard criteria. Finally the subjects were asked to write down a description of their experience on the evening of the experiment.

OBSERVATIONS

To the observer, the Sernyl experience varied to some extent with each subject, yet the following account of the experience noted down as it occurred, contains all the essential features. (A more general account is contained in the next paper.)

Minutes

- 0 Injection of 6.4 mg. commenced and given over five minutes.
- 2 "I feel as if I had had a few drinks—but not too giddy."
- 3 "I can't think clearly or easily."
- 4 "I feel a bit remote—I can hear—but I can't form my words properly. I feel a long way away—it's funny—but quite pleasant—it's odd—like a few whiskies—my voice seems to have a different sound to it—as if its reverberating."
- 5 "Your voice seems deeper—there is a hum in the room. I feel tired, as if I were falling asleep—your voice seems louder."
- 7 "It's strange—a sort of humming is heard—there is an odd feeling—I feel very tired—yet everything seems more acute—I'm sure I can hear a hum—like a reverberating hum—my voice sounds different."
- 9 "My limbs feel heavy and tired. That pin-prick is blunt—it just does not hurt—it's as if my senses are blunted."
- 11 "I don't feel able to control my movements properly—and the humming noise is still there."
- 12-20 Psychological testing carried out.
- 21 "My hand seems small—I can't seem to answer the proverbs properly—I feel as if I am talking from a long way away. I can't seem to think straight—I don't know why but I do know I can't do it."
- 22-30 Further testing.
- 31 "I feel a bit giddy—not unpleasant—it's difficult to describe—the pin is still blunt and my hands seem small—it's my fingers that are shortened and there is a vibration in all my fingers."
- 33-43 Further testing.
- 44 "My senses seem much more acute now. It's not pleasant, not unpleasant—I feel indifferent—and when I try and express things something stops me."
- 45 "I still feel that humming in my arms—like electricity."
- 46 "It seems so stupid—the proverbs seem stupid—I feel you are a long way away and I am indifferent to it—I can't think in a rational way."
- 48-60 Further testing.
- 61 "I feel more myself now but I am giddy when I move—it's better lying down."
- 62 Further testing.
- 75 "Things seem more normal now—the pin-prick feels sharper—things are now more acute."

Thereafter there was a gradual decrease in symptoms. At 100 minutes his hands appeared normal, and two hours after the injection, he was able to walk to the canteen for lunch, and he appeared normal to other people. He, himself, felt a little tired for another two to three hours and then was quite symptomless.

While the above could be taken as a typical example of the experience produced with Sernyl, in four patients "body image disturbances" were much more marked. Comments made at the time by these subjects were, "I feel very, very small—I'm tingling all over—small, small, small, going down—my hands do not look a part of me—it's horrible—everything looks narrow—it's odd—it's horrible—things seem a long way away—I feel numb all over—nothing feels part of me—it's terribly peculiar—you look miles away."

Another subject commented, "I feel to be floating away from everyone—it's unreal—things are distorted—you seem far away and bizarre—I seem to be floating off—I feel to be whizzing around, around and around—my hand looks distorted but it does not seem to be real—I feel detached from it all—I feel relaxed and my body detached and distorted from me. Everything has become enormous, fuzzy and one dimensional—flat—everything seems flat, as if cut out of cardboard—it's very bizarre."

One subject passed into a catatonic state. She complained of pins and needles in the limbs and face as the injection was given, and then for 23 minutes lay with her eyes opened, smiling, but unresponsive to questions. Then, at 23 minutes, she said, "Hullo—September—what is September?" Thereafter her account was similar to that described above.

While the acute symptoms subsided after 1-1½ hours, for several hours there was some unsteadiness on walking and most subjects felt generally "not quite right" for the rest of the day.

In four subjects, vomiting occurred—without nausea—and persisted for ½-3 hours.

Most subjects, for some hours after the experience, felt somehow detached from others and one commented, "Over lunch I had the odd feeling of lacking empathy with the whole human race—people's talk, their actions, lacked the genuineness and warmth of the old life." This detachment was commented on by several different observers who had dealings with the subjects later in the day.

Neurological changes occurred in each subject—there was a diminution of pain, touch and position sense. All showed nystagmus and were ataxic. One patient became diplopic.

The accounts produced for us during the evening of the experience show similar remarks, some of which will be added.

"I never really lost consciousness but sensations were viewed, somehow, from inside my skull—verbalization and evaluation were extremely difficult—then I felt like a flat worm—my head felt solid but below that I felt flat—like a huge skin rug—though if I looked at myself I saw in three dimensions. After a while, it all seemed a bit of a joke and I felt I had to entertain the tolerant audience."

"I can only account for very few thoughts—I do not know what happened in the first twenty minutes." (This is the subject who became catatonic.) "Thoughts seemed slow, quite clear, but isolated. Everything seemed unrelated and I lacked motivation to co-operate—I felt calm but without pleasure and I felt very slow about everything I did."

"The feeling was neither pleasant, nor unpleasant but peculiarly indifferent. Whilst I retained some insight—I could not think clearly on abstract

topics—my mental processes seemed slow and as well, there was an unwillingness to think, an indifference to the whole proceedings.”

“There was a roaring sound in my ears—everything went round and round, then things looked very strange—flat—one dimensional—I felt remote, with a feeling of loss of emotional contact. My body felt huge and lifeless—my hand seemed remote, huge. At one moment there was a terrifying feeling of impending dissolution—I could not think actively, organize, relate in any way—I could not discriminate what to attend to. I also felt rather truculent and somewhat disinhibited.”

“I had a feeling of falling down and getting smaller and smaller at the same time. When asked to open my eyes the room did not seem noticeably to have changed its size, but during the experiment, the nearest experimenter appeared to be a rather odd shape and size, his face especially seeming out of proportion and not similar to how I had previously seen him. I had to keep touching myself—my face, arms and hands. I knew they were mine and still there, but they felt very odd and as though they did not belong to me. I became very frightened of my hands at one point—they seemed very thin, bony (old) and apart from me. Another time my arm really felt very ‘narrow’ and made up of only two bones.”

“There was no adequate ability to analyse a problem, break it down into component parts and then consider these serially—a series of words presented for learning were accepted as a temporal series but the ability to learn them in the sense of forming meaningful connections between words was totally lost.”

“It is very difficult to account for the whole hour of the experience. I remember the injection, then I felt confused and ‘delirious’. I remember repeating things and having difficulty in following what I was asked to do. I seemed to come back to normal in waves. Later that day I felt listless, affectless and, later still, my head felt muzzy and this was made worse by movement.”

To sum up, the cardinal features described by Luby *et al.* (1958) were all observed—i.e., body image changes, estrangement, disorganization of thought, negativism and hostility, drowsiness and apathy, hypnagogic state, feeling of inebriation. Finally it may be noted that, except for the subjects who vomited, the experience was not unpleasant and most subjects were willing to repeat it if required.

PSYCHOLOGICAL TESTING

The selection of psychological tests was determined by three considerations. First as objective checks on clinical observations of reactions to the drug; secondly by diagnostic considerations; and thirdly as a means of comparing reactions to Sernyl and barbiturates.

These tests were usually administered before the drug was given, some fifteen minutes after the injection, and at subsequent intervals up to 1½ hours after the injection. No individual was given the complete battery of tests.

Size Estimation

Two tests were employed in obtaining size judgments. The first of these comprised 7 cards (5 inches×3 inches) each bearing a single circle. Only one of these circles was the diameter of one penny; three cards bore circles which were 2, 4 and 6 mm. larger, and three bore circles which were 2, 4 and 6 mm. smaller than one penny. The subject's task was to identify the card bearing a circle of the same size as one penny.

A similar task, involving identification of a card bearing a line one inch long, was also employed.

The data reported in Table I was obtained both before and 20 minutes after the injection.

TABLE I
Size Estimation

Condition						Plus	Zero	Minus
Non-drug	..	..	..	..	..	7	4	1
Drug	..	..	..	..	..	9	3	0

"Plus" indicates a judgment erring in the direction of choosing a stimulus larger than one inch or one penny. "Minus" indicates the opposite tendency. "Zero" indicates a correct judgment.

This data, obtained on six individuals, suggests that both in drug and non-drug conditions, there is a tendency to make errors of over-estimation of size. Omitting the "minus" entries and computing χ^2 for "plus" and "zero" entries under the two conditions, indicates that the trend further to exaggerate the tendency toward over-estimation under Sernyl is non-significant.

Area of Motor Response

A further effect, which may be related to size-over-estimation, is that of area covered in handwriting. This effect was examined in four individuals both before and after drug administration, when they were asked to write their full names and the words "United States of America". A rough index of area covered was found to be the overall length of the words written.

Three out of the four S's showed marked tendencies to increase the area of writing; the remaining subject showed slight changes in the opposite direction.

Tapping Speed

There is considerable evidence that slowness, both cognitive and motor, is produced by mental disorder (Foulds, 1951; Huston and Shakow, 1937; Nelson, 1953; Shakow and Huston, 1936). One might, therefore, reasonably expect that administration of Sernyl, if it produces some of the dysfunctions characteristic of schizophrenia, would result in impairment in motor speed and, in particular, that tapping speed will show decrement.

The test involved S. tapping as quickly as possible with a stylus upon a metal plate for a 10-second period. The number of taps was recorded on an automatic counting device. Two 10-second trials were given.

Seven S's were tested before and after the injection, the scores on each occasion of testing on the two trials being very consistent. The scores obtained under the two conditions and shown in Table II indicate that all the individuals tested became slower under the drug condition, the trend being significant at an acceptable level ($t=2.090$).

TABLE II
Tapping Speed

Subject							Non-Drug	Drug
1	..	..	..	..	..	..	98	82
2	..	..	..	..	..	..	111	87
3	..	..	..	..	..	..	118	92
4	..	..	..	..	..	..	104	93
5	..	..	..	..	..	..	112	74
6	..	..	..	..	..	..	113	103
7	..	..	..	..	..	..	81	79

The figures in the table represent the sum of the number of "taps" on two 10-second trials.

Spiral After-Effect

There is evidence which suggests that an organic condition may reduce the duration of the after-effect on the Archimedes Spiral (Holland and Beech, 1958). It has also been reported that barbiturates may reduce the duration of the after-effect (Eysenck, H. J., Holland, H. C., Trouton, D., 1957), and it was mainly for this last reason that the measure was employed.

Only three subjects were tested both before and after the drug; two other individuals could not be tested after taking the drug because of feelings of nausea. The three subjects tested were given two trials under each condition, the results being presented in Table III.

TABLE III
Spiral After-Effect

Subject						Drug Condition	Non-Drug Condition
1	..	..	..	..	..	0	23
2	..	..	..	..	..	6	21
3	..	..	..	..	..	32	46

The figures above refer to the total duration of the after-effects in seconds, on two trials.

It will be seen that all three S's showed decrement, and it seems reasonable to suggest that Sernyl probably has the same general effect as barbiturates where certain functions are concerned.

Critical Flicker Fusion

Critical flicker fusion thresholds are known to be sensitive to a wide range of influences, in particular the effect of barbiturates on this function is to reduce thresholds for the perception of fusion.

Seven of our S's were tested before and approximately 30 minutes after the administration of Sernyl, the thresholds under both conditions being established on "up" and "down" trials (i.e. from "flicker" to "fusion" and *vice versa*).

All S's tested in this way showed changes in the direction of lowered thresholds—i.e. required a lower rate of flicker in order to perceive fusion under the influence of Sernyl ($t=3.868$). This change, as pointed out above, is in the same direction as that which is produced by the action of barbiturates.

Time Estimation

In this test S's were asked to estimate 10, 15 and 20 second intervals under drug and non-drug conditions. Each of 11 S's was given three trials on each time interval under both conditions.

The results presented in Table IV indicate a general trend for the S's to over-estimate the time intervals under non-drug conditions, and to under-estimate the intervals under the influence of Sernyl. Here, over-estimation

TABLE IV
Time Estimation

						Drug	Non-Drug
No. of over-estimations	..	..	..	..	..	11	24
No. of under-estimations	..	..	..	..	..	22	9

Table showing number of judgments falling into the categories "Over-estimation" and "Under-estimation" under the two conditions.

refers to the tendency to judge that the interval has passed when, objectively, a longer time interval has elapsed; under-estimation refers to the tendency to judge a given time interval to have passed when, objectively, a shorter interval has elapsed.

A chi-square of 10.28 was obtained for the data presented in Table IV, indicating a real difference between the two conditions respecting time estimations.

Interesting trends were also noted respecting time estimation for those S's tested repeatedly following the administration of Sernyl. In Figure 2 these trends for one individual are reproduced, the three curves representing judgments of 10, 15 and 20 second intervals. These curves indicate a progressive degree of under-estimation up to 90 minutes after the injection, followed by a recovery period which, presumably, would have continued up to the average judgment for the non-drug condition had measurements been continued.

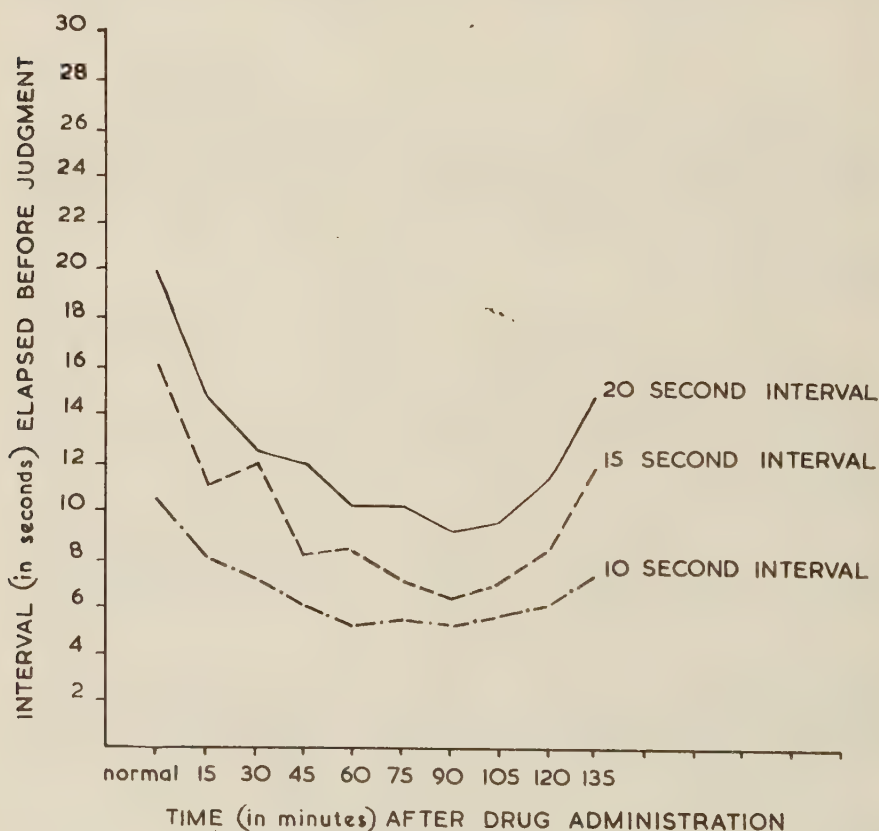


FIG. 2.—Individual time judgments at varying intervals after taking Sernyl.

Learning

It was of interest to examine the effects of Sernyl upon learning and recall, and to this effect two of our S's were tested using auditory paired associates.

Both S's experienced extreme difficulty in learning three "difficult" paired associates (e.g. Judge—Bowl), but had no trouble with "easy" pairs (e.g. Stop—Start).

Results obtained from one of our S's suggested that, in addition to producing a difficulty in learning new material, the drug might disrupt newly-formed associations. For this individual five pairs of numbers and letters were presented (e.g. M—6, S—2) and learned to a criterion of three correct reproductions.

This learning took place immediately before the injection, and recall of the material was obtained approximately 15 minutes after the injection. It was found that substantially more trials were required to reach the criterion during the recall period than during the initial learning, although one would ordinarily have expected the opposite to be true.

A further interesting point which emerged during the "recall" period in the S. referred to above was that some "incorrect" responses seemed to represent a recapitulation of "old" learning—e.g. the response "5" was repeatedly given to the stimulus letter "V" instead of the "correct" response of 7.

Proverbs

The test of the ability to state the meaning of proverbs was given partly in order to obtain a rough assessment as to loss in cognitive efficiency and partly because some authors believe that a schizophrenic disorder produces impaired ability correctly to define proverbs (Gorham, 1956).

The responses of individuals under Sernyl to Gorham's list of proverbs were extremely variable; all seemed to experience more difficulty in expressing their thoughts when under the drug and this difficulty was most marked in some cases.

In general it took much longer for a S. to explain the meaning of a proverb under Sernyl than in a normal state. Some responses obtained under the drug condition were extremely "concrete"—e.g. one individual's answer to the proverb "New brooms sweep clean" was "Of course new brooms sweep clean . . . they have longer bristles . . . old brooms are worn and don't make a good job of sweeping".

This degree of concreteness was, however, infrequent in our sample. Nevertheless, there was a tendency to produce answers of poorer quality under Sernyl than would ordinarily be expected from a sample of individuals all of whom were of high intelligence.

CONCLUSION

Although these findings must be regarded as essentially tentative, they suggest that certain interesting dysfunctions and changes in function appear under the influence of the drug used.

Some of the effects noted suggest that, on certain psychological tests, Sernyl acts in the same way as barbiturates. Other findings reported would indicate that the effects of this drug are not incompatible with effects produced by a schizophrenic process, although there is a decided lack of positive evidence for this drug as a schizophrenomimetic agent.

More systematic and detailed investigations of Sernyl are clearly indicated.

DISCUSSION

There can be no doubt that Sernyl produces a syndrome of great interest to the psychiatrist and psychologist. Intravenously, in the dosage used, the acute effects begin at once (unlike LSD) and are over within an

hour. Though general malaise then persists for several hours, this relatively short period of disturbance is very convenient for the study of a model psychosis. Many of the symptoms and signs produced are similar to those that occur with other psychoticomimetic drugs and some of these have been contrasted in Table V. It will be seen that it is the absence of hallucinations that

TABLE V

Cardinal Symptoms and Signs Produced by Some Psychoticomimetic Drugs and Sensory Deprivations

			L.S.D. (Stoll, 1947)	Mescaline (Tayleur Stockings, 1940)	Hashish (Berringer, 1932)	Sernyl	Sensory Depriva- tion (Bexton <i>et al.</i> , 1954)
1. Onset of symptoms	..	..	Within $\frac{1}{2}$ -hour (Orally or I.V.)	Within $\frac{1}{2}$ -hour	2-3 hours	Immedi- ate I.V. 1-2 hours orally	Variable
2. Prominent symptoms last	..	..	8 hours	10-12 hours	6-8 hours	1-2 hours	Up to 1 hour
3. Hallucinations:							
(a) Visual	..	..	+++	+++	+	+	++
(b) Auditory	..	..	++	++	+	0	0
(c) Somatic	..	..	+	++	+	+	+
(d) Tactile	..	..	0	0	+	0	+
4. Hyperacusis	..	..	++	++	+	++	++
5. Body image disturbances	..	..	++	++	++	+++	++
6. Depersonalization	..	..	+++	+++	++	+++	++
7. Disturbances in time appreci- ation	..	..	+++	+++	++	+++	++
8. Mood:							
(a) Euphoria	..	..	+++	++	+++	++	+
(b) Depression	..	..	++	++	+	0	++
(c) Fear	..	..	++	++	++	0	++
9. Behaviour:							
(a) Restlessness	..	..	+++	+++	+++	+	++
(b) Catatonia	..	..	+	++	+	+	0
10. Thought Processes:							
(a) Slowness and difficulty in concentrating	..	..	+++	+++	++	+++	+++
(b) Perseveration	..	..	+	+	+	+++	0
11. Delusions	..	..	++	++	++	+	+
12. Physical Signs:							
(a) Dry mouth and lips	..	..	+++	+++	+++	++	++
(b) Nausea	..	..	+++	+++	++	+	0
(c) Vomiting	..	..	++	++	++	+	0
(d) Tremors	..	..	+++	+++	+++	++	+
(e) Increased deep reflexes	..	..	+++	+++	+++	+++	+
(f) Nystagmus	..	..	0	0	+	+++	0
(g) Dilated pupils	..	..	+++	+++	+++	+++	0
(h) Diminished pain+temper- ature appreciation	..	..	++	+++	0/increased Sensitivity	+++	+
(i) Diminished proprioception	..	..	+++	+++	0	+++	+
(j) Respiratory changes	..	..	++	++	++	0	0
(k) Cardiovascular changes	..	..	+	+	++	0	0

KEY:

0=Does not occur.

++=Often occurs.

+=Occurs occasionally.

+++ = Usually occurs.

is the main distinguishing point between the model psychosis produced by Sernyl and LSD and mescaline (though as Meyer *et al.*, 1959, report, at doses of more than 10 mg. hallucinations do occur). Luby *et al.* (1959) commenting on this, suggest that the symptoms produced by Sernyl and certain primary symptoms of schizophrenia, may have a similar basis, and suggest,

as a tentative hypothesis, that they may arise from a dysynchrony or defect in proprioceptive feedback mechanisms.

Consciousness is altered in the model psychoses, yet it is difficult to define this alteration. Mayer-Gross, Slater and Roth (1955) writing of the state of consciousness in mescaline intoxication, say, "It is difficult to classify the state of consciousness during the intoxication which allows of such full self-observation and, at times, seems to foster detachment and self-scrutiny. At other times, the same subject seems to have lost all clarity of consciousness, is drowsy and even close to sleep. The continuity of consciousness may be disrupted and fragmented. Single impressions are dissociated and without connection at one time, and, at another, everything seems to flow in a unified stream of deep significance and importance, related in some way with the whole past life of the subject, who identifies himself with it. The breadth and capacity of consciousness may also be changed, constricted to a single small impression, as when one subject said that for him, the whole world was contained in "a fluff of dark wool on the doctor's white coat". In the dosage used, Sernyl usually affects the clarity of consciousness, though often, there are brief episodes of clear consciousness. "Self-scrutiny" was described by three subjects, and the significance of small, everyday objects, by two. In general, there is nothing like "the extraordinary faculty for self-observation and introspection" that Stockings described with mescaline. This would appear to be another major difference between the model psychoses produced by Sernyl and mescaline. The differences between the experiences of a patient who received both LSD and Sernyl, are described in the following paper.

Meyer *et al.* (1959) believe that Sernyl produces a form of sensory deprivation and suggest that the drug acts primarily on the sensory cortex, brain stem and thalamus. They contrast this centrally mediated sensory deprivation syndrome with that produced by depriving subjects of all external stimuli (Bexton *et al.*, 1954). The symptoms produced by this latter technique vary considerably from one subject to another. The resemblances and differences between these syndromes need to be studied further before final conclusions can be made. It is noteworthy that schizophrenics are made worse by Sernyl (Luby *et al.*, 1959) yet they may be tolerant of external sensory deprivation; indeed, hallucinations are reduced in intensity in some patients (Harris, 1959).

This study has suggested that each aspect of the Sernyl experience should be systematically investigated, using objective measures, preferably in intelligent volunteers who have no psychiatric knowledge. Specific hypotheses should be formulated and then tested so that comparisons can be made between the effects of Sernyl and other drugs (particularly LSD and barbiturates); the effects of Sernyl and sensory deprivation; and the effects of Sernyl and the primary symptoms of schizophrenia. In view of the report by Luby *et al.* (1959) that chronic schizophrenics were made worse by the administration of Sernyl and that this deterioration persisted for some weeks, it would seem unwise to repeat this observation, though it might be considered justifiable to administer the drug to patients who have made a good recovery from a schizophrenic illness of short duration. The effects of suggestion in producing accessory symptoms (Abramson *et al.*, 1955) should be clearly defined and, if possible, these symptoms correlated with personality variables. The modification of the Sernyl experience by tranquillizing drugs is also an important subject for investigation as is the study

of other drugs of the cyclohexylamine series. Some of these investigations are now being made.

SUMMARY

The drug Sernyl is described and the relevant literature reviewed. It was the first of a cyclohexylamine series introduced into anaesthetic practice because of its ability to produce analgesia without loss of consciousness. Post-operatively, however, psychiatric disturbances were common and the use of the drug in anaesthetic practice was curtailed. The drug appears to act at the thalamic level and produce changes in the reception of sensory stimuli. The effects on twelve normal volunteers are described and these contrasted with other psychoticomimetic drugs. As a result of this pilot study, possible lines of research are mentioned. As its action is relatively short, the syndrome produced is convenient to study from the psychological point of view.

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ON THE PSYCHOPATHOLOGY OF SCHIZOPHRENIA*

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IN this paper it is my intention to review some of the central aspects of the psychopathology of schizophrenia. At the outset it would be appropriate to establish the role which psychopathology must play in our efforts to arrive at a fuller understanding of the schizophrenic psychosis. Psychopathology is, as the term itself reveals, a psychological study of abnormal mental functions. It is not primarily concerned with the organic bases for the disturbance of mental activity, but such a study does not imply that the roots of abnormal psychological processes do not in fact lie in somatic pathology. To my mind psychopathology and studies of disturbed brain function in mental disease are complementary to one another. Many distinguished workers in the field of the psychoses have referred to the disappointing results of biochemical and electro-physiological research in schizophrenia. They have suggested that the failure of such research has arisen in part from the absence of correlation between clinical studies on the one hand and physiological studies on the other. Tait (1958) has remarked that although physiological research can provide us with a wealth of data this data will only become meaningful whenever clinicians are in a position to provide biochemists and electrophysiologists with sets of specific questions. The formulation of such questions must depend upon a refinement of our diagnostic categories. Similar criticisms have been levelled against psychological research. In a recent review of contemporary psychological research Rabin and King (1958) have pointed out that the lack of criteria necessary for the selection of a homogeneous group of patients leads to the vitiation of much current psychological research. It is possible that psychopathology may be able in the future to contribute something to the solution of these methodological difficulties which so beset and hamper contemporary research in schizophrenia.

GENERAL PROBLEMS OF PSYCHOPATHOLOGY

There is a frequent and understandable tendency to conceive of psychopathology as solely concerned with psychological explanations of symptom formation. Such explanations generally utilize concepts derived from psychoanalysis. The concept of an unconscious mental conflict which leads to a failure of repression and thus to the symptoms of a psychoneurosis is a good example of a theory which explains the occurrence of a specific form of mental illness.

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Here we are dealing with an important aspect of psychopathology—one which emphasizes the dynamic character of mental processes. However, psychopathology must be thought of as embracing a much wider view of mental activity in disease if we are to do justice to this important subject.

Psychopathology is also concerned with the form which mental processes take in disease. The altered states of consciousness and the thought disturbance in schizophrenia, the depression of mood in melancholia and the abnormalities of perceptual processes which occur in most psychotic states are all within the province of psychopathology. Reference to certain textbooks of psychiatry reveals that these phenomena are described in the chapter entitled psychopathology. In these accounts we are presented with a description of the form which the conscious mental processes have assumed under the impact of the disease. Today we are not satisfied with a description of such psychopathological phenomena alone. We look for an explanation of these subjective experiences in terms of mental conflicts of which the patient is unaware. We postulate differing mental contents involved in the conflicts depending upon the nature of the symptoms and the ideas which can be inferred from the patients' communications about his mental life. Here we are no longer concerned with the registration of the patient's conscious mental processes but with the construction of psychopathological hypotheses of the type to which I initially referred.

During the past years psychopathological theories have increased in number and complexity. In most cases they are concerned with the content of specific unconscious phantasies. We generally find that a theoretical relationship is established between the signs and symptoms of the disease and these unconscious phantasies. In these formulations which are very frequently concerned with schizophrenia psychopathology is identified with unconscious dynamic mental processes which are conceived of as playing the decisive role in symptom formation. Other characteristics of mental activity are either ignored or relegated to a position of minor importance.

In his theoretical papers Freud (1915, 1916) declared that mental processes were not adequately described unless the description included their location (the topographical aspect), their energetic charge (the economic aspect) and their relation to mental conflicts (the dynamic aspect). Such a comprehensive account of mental processes is not easy to formulate in either health or disease but it is an ideal at which we should aim. In doing so we no longer limit the subject of psychopathology either to a description of the form of conscious mental states in disease or to hypotheses which are limited to the concept of unconscious mental conflict. Psychopathology should extend beyond such narrow confines.

In schizophrenia we are presented with phenomena which are completely different from the mental processes of the healthy or neurotic individual. Such phenomena are not necessarily encompassed by the patient's awareness in consequence of altered states of consciousness. Sometimes they only manifest themselves in behavioural activity. In order to obtain a comprehensive account of the formal aspects of a mental disturbance it is essential to possess some knowledge of the form which primitive and undeveloped mental processes assume. The possession of this information sometimes allows us to recognize and differentiate the varied clinical manifestations. In paying such close attention to the form of mental processes we are following a basic principle of natural science—namely the description and classification of phenomena. In contrast to most psychopathological formulations which emphasize unconscious content

we are freed from the difficulties which follow upon abstraction and inference from clinical data. The leap from clinical observation to psychopathological theory is a dangerous one. We know that different observers can, in accordance with their theoretical predilections, present two entirely different psychopathological explanations from identical clinical material. This has not led to an increased confidence in the value of psychopathology. Perhaps one way out of the present impasse is to retrace the steps taken by Schilder (1923) who attempted to find meeting points between psycho-analysis, experimental psychology and genetic psychology in the hope that it might lead to a deeper knowledge of what he called "the formal structure of the psyche" (Schilder, 1923).

FORMAL ASPECTS OF "PRIMITIVE" MENTAL PROCESSES

The description of primitive and undeveloped mental processes has been accomplished by two methods. First place must be given to the psycho-analytic method. By its discovery Freud (1900, 1913, 1915) was able to describe the characteristics of unconscious mental processes and note their similarity to the mental activity of young children and primitive peoples. This discovery led in turn to the second method—the direct observation of young children and primitives.

Much of Freud's theoretical writings contain references to what has been described as the primitive thought process. In the theoretical chapter of *The Interpretation of Dreams* (1900) and in other works he was less preoccupied with the specific characteristics of this form of mental life than with describing a hypothesis which would adequately account for its functioning. He called the mechanism which he hypothesized the primary process in contrast to the secondary process which governed the action of conceptual and reality adapted thinking. Nevertheless one characteristic of primitive mental processes becomes apparent after the shortest acquaintance with the study of dreams—namely the prevalence of imagery. Freud (1900) understood very early that the hallucinatory quality of dreams resulted from the replacement of ideational content by sensory images. A consequence of this appreciation was the recognition by Varendonck (1912) of the manner in which concepts are replaced by concrete images during states of fatigue and prior to sleep. As Freud (1923) points out "Thinking in pictures, is, therefore, only a very incomplete form of becoming conscious. In some way, too, it approximates more closely to unconscious processes than does thinking in words, and it is unquestionably older than the latter both ontogenetically and phylogenetically".

On at least two occasions (1913, 1915) Freud described in some detail the general characteristic of unconscious mental processes. In *Totem and Taboo* (1913) he showed how clearly these unconscious processes resemble the mental activity of young children and primitive peoples. He established the general principle that unconscious mental life is typified by the supremacy of psychical over external reality. The ideas of things become more important than things themselves. This over-valuation of mental processes in comparison with reality Freud (1913) described as the omnipotence of thoughts. The consequence of the primacy of thought leads to a form of logic—magical thinking—which ignores the difficulties of time and space. As Freud (1913) puts it "... the world of magic has a telepathic disregard for spatial distance, and treats past situations as though they were present".

Psycho-analysis has had the virtue of turning the attention of psychologists

to the problems of mental development particularly as they apply to the cognitive functions. Today genetic psychology is one of the most extensive branches of psychology and Werner's name stands out as one of the leading figures in this field. It is to his work that I will principally refer in the following brief account of childhood mental processes. Werner (1957) characterizes primitive mental activity as syncretic. By syncretic he refers to a form of mental organization in which the various mental processes are not clearly differentiated from one another. Let us first turn to Werner's (1957) account of primitive perceptual function to illustrate his concept of syncretism.

Research undertaken by genetic psychologists indicates that the young child perceives in quite a different manner to the adult. In the case of visual perception the child perceives the dynamic aspects of an object rather than its static qualities—a dog, for example, is something that barks or bites. Inanimate objects are regarded as manifesting similar motor and affective attitudes as the child experiences himself. Werner (1957) refers to this form of perception as physiognomic as it is utterly different to our everyday adult perception in which things are known in accordance with their geometrical-technical qualities. Childhood perception is syncretic in that it is inextricably linked with affect and motor behaviour. This is nowhere better seen than at the cinema or television show. Young children watching an exciting "Western" could be said to perceive with their bodies. Unlike the adult, who may only indicate his reaction in his facial expression or by the slightest movement, the child's whole being is involved in the perceptual process.

A further characteristic of primitive perception is its undifferentiated nature. The different sensory modalities have a closer relationship at the primitive level. The term *synaesthesia* denotes the phenomenon of a specific stimulus arousing not only the corresponding sensation but a second sensation also. A common instance is colour-tone *synaesthesia*, as when the perceiving individual sees colour while listening to tone. According to Werner (1957) *synaesthesia* should not be looked upon as a bizarre and abnormal mode of perception. He believes that it is bound up with the development of the faculty of perception.

Before leaving our consideration of primitive mental processes we must give some attention to the mode of thought appropriate to this developmental level. As in the case of perception the primitive thought process is fused with affect and with the sensori-motor functions. It is syncretic in nature. Let us take as an example one form of primitive thinking—namely primitive abstraction. This can be observed when young children between the ages of 3 and 5 are asked to select from a number of red triangles and green circles those figures which are the "same" as a standard form. This standard may be either a green triangle or a red circle. The children unhesitatingly make a selection based on colour. Their selection is not determined by the shape but upon a tendency in perceptual organization to bring together those elements which show a perceptual similarity. This attraction of a common property of objects is characteristic of primitive abstraction. This form of thinking, therefore, is closely tied to a mode of perceptual (sensory) organization which is less concerned with the details of the perceived object than with qualities which dominate and permeate the totality. This kind of primitive abstraction is to be observed in the utterances of young children. Werner (1957) quotes the case of a child of 3 years of age who sees a painted landscape with a boat in it, and says "It's summer now!" even although it is a winter scene which is represented in the picture. The boat dominates the child's experience and determines the meaning of the entire

scene. During the course of development the child frees himself from this form of abstraction. He comes to perceive that objects have different qualities any one of which may be taken as the point of departure for an ordering process.

THE CONTRIBUTION FROM EXPERIMENTAL PSYCHOLOGY

Recent research by experimental psychologists in the perceptual field has, to my mind, a special relevance for a psychopathology of schizophrenia. The work to which I will refer springs from two sources. The first, associated again with the name of Werner, is concerned with an experimental study of the syncretic tendency in perceptual processes as they occur in adult and child. The work of Fisher (1954), Klein (1959) and others on subliminal perception provides the second contribution which experimental psychology is currently making to the study of abnormal mental processes.

I

Werner and Wapner (1952) have devised experiments to test the conclusions which they have drawn from their observations of the perceptual function in children and in primitives. Believing that perception at such developmental levels is intimately linked with motility—an aspect of its syncretic nature—they have devised experiments to support or weaken this hypothesis. In these experiments Werner and Wapner (1952) examined the effect of body tilt on the perception of verticality. A large number of subjects of varying age were required to adjust a luminous rod in the dark to a position in which the rod appeared vertical, while the subject's body position was tilted 30° from the vertical position. Adult subjects and older children perceived the rod as vertical when it was in a position opposite to the side of the body tilt. Younger children, however, particularly those below the age of nine, perceived the rod as vertical when it was in a position relative to the side of the body tilt. This observation is cited both to support the theory that childhood perception is influenced by motility and to illustrate the developmental principle of the gradual differentiation of the self from the environment. It is also in accord with Piaget's (1947) view that spatial order for the child is dependent upon body position.

In further experiments Werner and his colleagues (1952) have demonstrated that visual perception is equally influenced by different forms of sensory stimulation. This suggests that a kind of "functional equivalence" (Werner) exists between the different sensory modalities. In one set of experiments Werner and Wapner (1952) presented subjects with an ambiguous pattern where either the left or the right side of the picture could be perceived as the figure. As the pattern was shown to the subject he was simultaneously presented with an auditory stimulus (a tone) in one ear. The results showed that the area perceived as the figure was dependent upon the side of auditory stimulation. When the right ear was stimulated the left side of the pattern was seen as the figure and *vice versa*. Thus extraneous stimulation of the subject in one sense modality produced a direct response in another sense modality. In other experiments perception of the vertical was equally affected by kinaesthetic and auditory stimuli. Further work of this kind with children indicated that this functional equivalence was even more pronounced in their case.

II

It is some years now since Poetzl (1917) demonstrated experimentally that the manifest content of dreams contains perceptual data which never reach consciousness. He also suggested that in psychotic states patients become aware of percepts which ordinarily remain unconscious. For some reason Poetzl's work was neglected until quite recently. However, in the past few years many reports have appeared confirming Poetzl's findings and describing the results of various types of tachistoscopic experiment.

There is now little doubt that the non-conscious registration of stimuli is a continuous process. Of particular interest is the work of Klein (1959) which has been concerned with the ways in which subliminal registration affects thought in the waking state. The results of his work suggest that subliminal registrations activate processes outside awareness which lead to different forms of verbal and non-verbal expression. Klein (1959) has proposed that the term subliminal perception is rather unsatisfactory. He has distinguished between the mental registration of sensory stimuli and conscious perception. To quote from one of his articles (1959) "The processes responsible for phenomenal registration seem to be independent of those which govern attention deployment—the means by which we become aware of things in a distinctive quality". In his opinion a stimulus which effects registration will only appear as a conscious percept when it is endowed with a special cathectic quality. At this point Klein appears to be following Freud's (1938) theory that "being conscious cannot be the essence of what is mental . . . it is only a quality of what is mental, and an unstable quality at that". Klein's experimental work indicates that the registration of sensory stimuli occurs on a wider and more indiscriminate scale than could have ever been imagined on the basis of observable reactions. Under normal circumstances it is relatively easy for sensory stimuli to enter the psychical system but they cannot so easily emerge in consciousness as either percepts or images. Klein conceives of "controlling structures" within the ego (i.e. the psycho-analytic ego) which determine the fate of the sensory registrations. It is reasonable to assume that the integrity of such "controlling structures" is essential if the function of attention is not to be at the mercy of extraneous sensory stimulation or of the imagery which arises from unconscious phantasy.

CLINICAL OBSERVATIONS

At this point I would like to present a number of clinical observations illustrating in the main the disturbances of thought and perception which can occur at different stages of the schizophrenic process. The majority of these observations were made during group psychotherapy. This method gives the clinician an unrivalled opportunity to observe inter-patient and patient-doctor interaction.

I

The first observations which I will report were made on a man of thirty years of age who was suffering from an acute schizophrenic episode. In a short time he had developed paranoid ideas and delusions of various kinds. While his thought processes were disturbed they were not so seriously impaired as to interfere with intelligible verbal communication. Thoughts had become reality for this man. In consequence he was convinced of his omnipotence. He was the centre of the world and the prime cause of all events. As an illustration of this

I will quote his statement that his stubbing out a cigarette had caused a man's death. He announced this shortly after reading of this event in the newspaper at the moment when he had put out a cigarette he had been smoking. In patients of this kind we are presented with a form of egocentrism—to use Piaget's term—which is almost identical with that of early childhood.

The next observations are taken from an entirely different category of patient—namely those patients whose illness has continued for many years without remission. In these patients we can detect the presence of a form of thinking which has been superseded in the healthy adult. It may, perhaps, be best compared with the primitive form of abstraction to which I referred earlier. The first example is brief. The patient was a young catatonic man of about 28 who had been ill for several years. He was rather negativistic but would reply when spoken to. He was undergoing psychotherapy and at the beginning of the treatment he was asked if he knew the season of the year. It was in fact a winter's day with snow on the ground but the sun shining brilliantly. The patient looked out of the window and without hesitation answered summer. I do not think this was a nonsensical or evasive answer. Can we not infer that his response had been determined by his awareness of the sunshine and that this percept had overshadowed any other facet of the observed situation. This reaction could be profitably compared with that of the child for whom the boat in the picture was the stimulus for his answer. This clinical example as in those to follow indicates the artificiality of discussing under separate headings the disorders of thinking and perception. They are so closely inter-related that the consideration of one implies the consideration of the other.

The tendency to abstract potentially communicable material on the basis of common concrete data can be clearly observed in chronic hebephrenic patients. This form of mental process is characterized by an apparent inability, on the patient's part, to assimilate a number of dissimilar facets of a whole object and to arrange them in order of importance. For the patient the part is as important as the whole. Clinical observation suggests also that the selection of the part is partly determined by affective factors. In the following examples the patient's communications were the outcome of an interaction between the patients and nurses and between patients and doctors.

Both of the instances which I will quote occurred during group psychotherapy. This particular group of female patients was conducted by two male doctors. The patient in question, a rather disorganized chronic hebephrenic, had been anxious in her relation with the therapists. Her conflict in this regard was expressed in the following communication—"I was frightened of two umbrellas in case their handles damaged me, so I stayed out in the rain. Now I'm not frightened any more and I shelter under the umbrellas." I think it reasonable to assume that the sexual factor (the transference in this case) does not account for the particular form of the mental process but determines its content. The choice of umbrella rather than some other attribute of the therapists must result from its unconscious phallic associations. In the second case the patient was forever referring to nurses as either "capes", "hems", "ruffs" or "waterproofs". This was particularly evident whenever she was angry. Here again we have an example of this primitive thought process which utilizes a common sensory impression in order to make a generalization.

II

The best known perceptual disorders in schizophrenia are the hallucinations and illusions. However, I will not refer to such phenomena here as it is my

purpose to direct your attention to other forms of perceptual anomaly. Periodically we are fortunate enough to encounter patients who are able to describe the manner in which their perceptual faculties are effected. On two separate occasions catatonic patients have reported that the perception of their surroundings was unusual and a source of fear. One patient said that she could not move "because things won't stay still and I'm afraid". A more lucid account of the same phenomenon is contained in the following remarks by a catatonic patient reported by Sechahaye (1956): "All the objects were transformed. I no longer recognized them. They suddenly took on other forms and I lost the only stability I had . . . I did not want to move, because if I did everything changed around me and upset me horribly so I remained still to hold on to a sense of permanence!" Such phenomena have something in common with the physiognomic perception which occurs in early childhood.

The next example is also concerned with the relationship between perception and motility. The patient was a young man of twenty-three years of age who suffered from catatonic schizophrenia. He spent many hours in a state of complete immobility. During treatment it became apparent that any movement was associated with visual perceptual distortion of the environment which he variously described as "a flatness", "a piece of stage scenery", "a flat streak of colour". Moving faster increased the severity of this disorder. It was noted that sudden changes in visual perception, brought about by sudden alterations in his visual field, always led to catatonic rigidity. This form of catatonic manifestation appeared not only in response to changes in visual perception but also as a result of an unexpected noise or to a rapid alteration in sounds already heard. This identical motor reaction in response to different forms of sensory stimuli suggests that in this patient's case there was an equivalence between auditory and visual percepts. This clinical observation can be compared with the experimental findings of Werner which I mentioned earlier. The equivalence of sensory stimuli noted in the laboratory was paralleled by the patient's remark that "A movement in front of my eyes is like hearing a sound in my ears". Here we are presented with a phenomenon which could be classed as synaesthetic. In these instances of disturbed visual perception there appears to be a return to the syncretic form of mental function where perceptual modalities are no longer discrete and where motility is no longer autonomous but is once again an aspect of an undifferentiated sensori-motor reaction.

In the clinical examples which are to follow I will describe yet another type of perceptual abnormality which has not received so much attention as it undoubtedly deserves. Bleuler (1924) has described this phenomenon as "a peculiar kind of distractibility". It occurs in cases in which a deterioration of the thought processes has taken place. He observed that during conversation patients will raise apparently irrelevant topics. This preoccupation can be traced to accidental sights or sounds which have impinged upon the patient's awareness. The group situation afforded an excellent opportunity to observe this "distractibility".

During treatment sessions my colleagues and I (Freeman, Cameron and McGhie, 1958) noted that some patients were inclined to incorporate what seemed to be random percepts into their stream of talk. During one meeting a deteriorated hebephrenic woman was talking rapidly and incoherently. At the other end of the room a colleague had said to another patient, "You think I only like married women". Without halting in her flow of speech the first patient said, "Yes, I like married women" quite unperturbed by the irrelevance of her comment. In my final example a patient of similar kind showed how

seemingly indifferent auditory percepts may be employed to provide ideational content which is used to convey allusions to the group situation. The patient in question had been asked what she had been doing at the weekend. Her reply was that she would have liked to have listened to the noise of the canvas. My colleague understood that this apparently bizarre reply referred to a canvas-type churn. Knowing that the patient's mother had such an implement at home he told her that she had longed to be at home during the weekend. When she was asked about her mother's cheese making the patient said that her mother made cheese for six cats. Immediately prior to this reply a cat had miaowed outside the window. The number six referred to the six patients in the group. The psychical processes operative in this example bear a close resemblance to the mechanisms of dream formation. As in dream formation there is the registration of apparently random sensory stimuli (the day residues) followed by a working over of the memory traces of the stimuli by the primary process. The instinctual wish that motivated the communication was surely the desire to be re-united with her mother.

A PSYCHOPATHOLOGY OF SCHIZOPHRENIA

Freud's (1923) concept of the ego provides us with a theoretical model which can be used when we try to work out a psychopathology of schizophrenia. From a topographical standpoint the ego comprises the organized area of the mind. This mental organization comprises a number of functions which enable the individual to adapt to his environment and to satisfy his basic needs. Amongst the most important functions are thinking, motility, perception, memory, reality testing and defence. The last-named function has the task of limiting the conscious mental expression of the instinctual drives. In this respect it expresses the dynamic character of the ego. The effective performance of the ego must depend upon somatic energy sources. This economic aspect of the ego has been the subject of much discussion both in normal and pathological states.

In schizophrenia we find that one or more ego functions are gravely disturbed. We must ask what sequence of events leads to the ego disturbance which we recognize as the symptoms of the disease? Psychopathological interpretations generally take a psychical conflict as their starting point. The conflict does not lead to symptom formation in consequence of a failure of repression, as in the neuroses but instead leads to a break with reality. A fundamental weakness in the ego is envisaged which renders it helpless in the face of inner dangers. This in turn results in a failure of function—particularly reality testing. A simple example would be the male patients whose unconscious homosexual conflict cannot be contained by the ego. The consequence of this is a failure of reality testing and a simultaneous projection of the unconscious homosexual wishes. The psychotic symptoms (the paranoid delusions in this case) now become a substitute for the unconscious conflicts and provide a defence against conscious awareness of the homosexuality.

This theory, initially proposed by Freud (1911), of a break with reality as the initial phase in a psychotic illness was challenged by Federn (1953). His extensive clinical experience with schizophrenic patients led him to propose that the break with reality was a secondary reaction. He believed that the first manifestations in the disease were due to perceptual distortions which then led to the break with reality. These perceptual abnormalities could often be traced to a psychic conflict. Federn's theory has two important implications.

First it suggests that the defect in schizophrenia is to be found in an ego which reacts anomalously to psychic or physical stress. Second it raises the possibility that the psychotic symptoms are not necessarily linked with an unconscious conflict nor is the aim of the symptoms the provision of a defence against the conscious recognition of the conflict.

The clinical data indicate that once the disease process is under way a regressive process occurs within the ego. It no longer functions on an adult level but on a plane similar to that of the young child. The instances which I have quoted, and the literature is full of them, illustrate this similarity. However, we are entitled to ask if regression is the only process at work within the schizophrenic ego. This question is particularly important because there is an inclination to conceive of all schizophrenic symptoms as being no more than the re-appearance of infantile mental processes, of infantile phantasies and their associated affects.

The researches of Klein and his colleagues (1959) allows the construction of a hypothesis which can account for some of the typical manifestations of schizophrenia without invoking the concept of regression. You will recall that Klein suggested that there exists within the healthy ego "controlling structures" which regulate the entry into consciousness of sensory stimuli which have already achieved a mental registration. When we observe the chronic hebephrenic patient as in the instances quoted we are presented with a situation not unlike that which Klein (1959) conceives of as occurring unconsciously in the normal individual. The patient indicates that he is aware of a deluge of percepts and images. These cases present an almost antithetical condition to that state of normalcy envisaged by Klein (1959) where "getting into the system seems to be less difficult than emergence in awareness".

Such clinical observations taken in conjunction with the experimental findings lead to an explanation of the phenomenon known as "splitting of the thought processes". It is conceivable that damage to the perceptual system of the ego leads to a failure of its screening function. As a result the individual can no longer insulate a train of thought from extraneous sensory stimulation. Percepts and images now compete for attention with the already existing thoughts. It is also likely that the perceptual disorder leads to an awareness of imagery which springs from the instincts. You will recall that in *The Interpretation of Dreams* (1900) Freud pointed out that a distinguishing feature between the primary and secondary process was the absence, in the latter, of mobile cathectic energy. This precluded, in secondary process thinking, the appearance of condensation products whose sensory vividness would seize attention and thus disrupt reality adapted thinking. This recognition by Freud of the potentially disrupting effect of the primary process is equally applicable to external stimuli. When the ego is damaged not only does the primary process become more prominent and provide an unusual source of internal perception which may interrupt thought but there occurs simultaneously a loss of the capacity to insulate thinking from the multiple sources of external stimulation. This hypothesis fits rather well with Schilder's (1923) theory that the schizophrenic is unable to pursue "the determinative idea" to which the normal person directs his thoughts on account of the fact that he is at the mercy of ideas and associations subsidiary to the main stream of his thinking.

Two distinct yet inter-related processes may be at work within the ego. The first is the regressive trend and the second is in the nature of a defect which effects such functions as perception and the defence mechanisms. In consequence of the former there is a re-instatement of child-like mental processes while as

a result of the latter there appear new forms of psychic phenomena which have never before had a mental representation. I think that we could classify the catatonic disturbances of motility under this category.

According to the approach outlined here we have in schizophrenia a mental organization which has suffered an injury of varying extent. The instinctual life—the sexual and aggressive drives—is expressed through the medium of this mental organization. Their manifestation will depend upon the ego level which has been reached in consequence of the disease process. We have seen, in at least one example, how the sexual drives determine the content of the mental process but not its form. Some of the clinical observations which I have cited suggest that there is a strong reaction against the disintegration of the ego. It would appear as if the patient is attempting to recover his capacity for stabilized thinking, motility and perception by insulating himself against stimulation arising from the environment. This would account for the reluctance and resentment which many patients show when invited to undertake activities or make human contacts. It is as if they feel themselves to be in a state of overstimulation and their desire is to reduce this to manageable proportions. Such an interpretation is supported by the observation (Harris, 1959) that when schizophrenic patients are subjected to sensory deprivation they find the experience more tolerable than normals. In some cases hallucinations were actually reduced.

We are now in a position to discuss the manner in which the psychological structure of the psychoses differs from that of the neuroses. In the latter the principal task is to remove by symptom formation any trace of the danger situation created by the failure of repression. In the former the symptoms have an entirely different function. They are not directly related to efforts directed towards an annulment of dangers created by the instincts but with efforts to restore the ego. Psychotic symptoms can be regarded, therefore, as having a stabilizing and adaptational role. They are, in effect, anomalous ego reactions. These reactions, arising from a mental structure whose function is defective, do not succeed in preventing the eruption of the primary process nor do they ensure a satisfactory adjustment to the environment. However, they do permit some kind of stabilization of the psychic economy. To my mind this is the one important factor common to the neurotic process and to that which occurs in psychosis.

PSYCHOPATHOLOGY AND CLINICAL RESEARCH

In this paper I have tried to discuss the psychopathology of schizophrenia from as broad a standpoint as possible. This has led to an interest in genetic and experimental psychology—subjects which have much to contribute to our understanding of mental disease. Clinical and laboratory observations are relatively worthless without a theoretical basis to which they can be related. For this reason we are forced to make use of theoretical constructs which give meaning and order to the observed phenomena. These hypotheses can, in the nature of things, only be approximations to the true state of affairs. Freud's metapsychological concepts (1900, 1915) can be of service in this regard. They will continue to be of service until the clinical and laboratory data demand their revision or dismissal. With their aid we are prevented from limiting the scope of psychopathology to dynamic formulations alone. At the same time

they make us aware of the necessity to study the nature of both conscious and unconscious mental processes.

Unfortunate as it may be we have to acknowledge the fact that clinical research can only become potentially meaningful when it is undertaken against a background of certain theoretical preconceptions whatever their nature. Recognition of this serious limitation allows us to place the subject of psychopathology on an equal footing with other aspects of psychiatry, as a legitimate contributor to clinical research. When we investigate a particular symptom complex or behavioural manifestation we not only want to know its relation to mental conflict but also its relationship to the different psychic systems. The economic or energetic changes which, we must presume, occur within the ego will remain for long enough in the realms of the hypothetical. For this reason I would be inclined to give them less attention.

An important feature of a psychopathological inquiry will be the assessment of the ego state. Study of the clinical manifestations can, for example, give us some notion of the state of the ego boundaries. I do not think that this is uniformly effected in all cases of schizophrenia. We can observe the extent of the perceptual abnormalities, the disturbances of thinking, of attention and motility. We will note the relationship which exists between these functions. I cannot believe that this information will be obtained from routine consultations, questionnaires or even personality tests. To my mind it will only appear in the context of interpersonal relations. It is here that group therapy has an important role to play supplementing the rich information to be obtained from the reports of nurses, occupational therapists and from individual psychotherapy. These interpersonal relationships will enable us to see something of the instinctual life which will be expressed on the ego level operative at the particular time.

I believe that there is an important place for clinical research of this kind. Much more "primary data" requires to be gathered before we can proceed to the elaboration of hypotheses which may be tested by experimental methods. It is to be hoped that in the future possibilities will exist for the integration of psychopathology with clinical research in psychiatry.

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SENILE SCHIZOPHRENIA

By

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THE author has already briefly reported on his investigation of senile paranoid states to the First Meeting of the European Clinical Section of the International Association of Gerontology (Fish, 1959a). He would now like to present his findings in more detail and discuss the relevant psychiatric literature.

In the Anglo-American psychiatric literature it is unusual to find the term "schizophrenia" being used to designate psychiatric illnesses which have begun after 40 years of age. It seems to be a standard belief in Britain and the United States that schizophrenia is a disease of adolescence and only rarely, if ever, occurs in the involutional period or in the senium (Henderson and Batchelor, 1956). Thus Victor and Hope (1958) when discussing the differential diagnosis of a group of hallucinating patients write, "In the former group, the symptoms began at 46-50 years of age, a range considerably beyond that usually encountered in schizophrenia."

It is customary to call the chronic paranoid psychoses, which occur in middle life, paranoid states or paraphrenia. It would appear that some English-speaking psychiatrists consider that paraphrenia can be differentiated sharply from paranoid schizophrenia. Mayer's (1921) follow-up study on Kraepelin's group of paraphrenic patients seems to be unknown and is only briefly referred to in one of the many textbooks of psychiatry written in English. Mayer found that many of Kraepelin's paraphrenics showed unequivocal signs of dementia praecox later in the course of the illness and that it was not possible to distinguish between the initial clinical pictures of those patients who finally developed obvious dementia praecox and those who did not.

Another common belief is that paranoid states in middle life are often due to coarse brain disease. This view has mainly been handed on orally, but has recently been expressed by Hill (1956) when he wrote "... in the involutional period of life organic cerebral factors, themselves unrelated to schizophrenia, usually act as precipitants of the psychosis and inevitably determine an unfavourable prognosis".

The views of German-speaking psychiatrists are quite different from those discussed so far. Thus Kraepelin (1913) using a fairly narrow concept of dementia praecox, which excluded paraphrenia, found that 5.6 per cent. of his series of 1,054 cases had an age of onset of 40 years or more and in 0.2 per cent. the illness began after 60 years of age. Carl Schneider (Kolle, 1931) in a series of 889 patients found that 16.0 per cent. had an onset after 40 years of age and 0.6 per cent. after 60 years of age, whereas Kolle (1931) in a series of 182 patients found 18 per cent. had an illness which began after 40 years of age, and none in whom it began after 60 years of age. Recently Müller (1959) has studied 101 unselected senile patients with schizophrenia and found that in 30 the illness had begun after 40 years of age and in 4 after 60 years of age.

M. Bleuler (1943) has investigated "late schizophrenia" which he defines as schizophrenia occurring after the age of 40 years and which conforms to the following criteria:

1. It should have occurred for the first time after 40 years of age.
2. The symptomatology should not differ from that of schizophrenia earlier in life or if it does differ it should not do so in a clear and radical way.
3. It should not be possible to attribute the illness to an organic disorder because of the presence of an amnesic syndrome or associated signs of neurological disease.

Bleuler found an incidence of 15 per cent. of late schizophrenics in a series of chronic hospitalized schizophrenics. The age distribution of Bleuler's series of 126 late schizophrenics is shown in Table I. This author also investigated the cause of death of 17 female late schizophrenics, who died in the

TABLE I
The Age Distribution of 126 Late Schizophrenias
(After M. Bleuler)

Age of Onset					No. of Cases	Percentage
40-44 years	..	..	..	..	44	35
45-49 years	..	..	..	..	42	33
50-54 years	..	..	..	..	20	16
55-60 years	..	..	..	..	15	12
Over 60 years	..	..	..	..	5	4

University of Basle Psychiatric Clinic. In 3 cases the brain was normal and death was due to pneumonia, in 4 cases the diagnosis of schizophrenia was wrong or doubtful since neuropathological changes were present which had affected brain function, and in 10 cases the lesions of the brain were present, which had obviously occurred a long time after the onset of the schizophrenia.

The present author's experience in British mental hospitals is in agreement with these Continental workers. In a series of 111 chronic female schizophrenics previously reported (Fish, 1958b), the age of onset could be fairly accurately determined in 110 cases. In 23 cases the illness began after 40 years of age and in one of these the age of onset was over 60 years. Since this series was a representative sample of chronic schizophrenics from all the female wards of an English public mental hospital with the exception of the geriatric ward then the incidence of schizophrenia in middle-aged and elderly females is probably greater than is suggested by these figures. The clinical pictures in the author's 23 middle-aged and elderly schizophrenics did not differ from clinical pictures occurring before the age of 40 years. The distribution of these cases in the different Leonhard sub-groups is shown in Table II. It will be seen that no case of catatonia, hebephrenia or schizophasia was found in those patients with an age of onset between 50 and 59 years but in 7 out of 9 of them auditory hallucinations were a prominent feature. It would appear that with the increasing age of onset schizophrenia tends to take the paraphrenic form, so that one would expect that senile schizophrenias would belong to one or other of Leonhard's sub-groups of paraphrenia.

TABLE II

Classification of 23 Cases of Schizophrenia with Onset Over 40 Years of Age

Leonhard Subgroup				40-49 Years	50-59 Years	Over 60 Years	Total
Affect-laden paraphrenia	..	..		2	1	0	3
Schizophasia	..	..	..	1	0	0	1
Speech-prompt catatonia	..	..	..	1	0	0	1
Autistic hebephrenia	..	..	..	1	0	0	1
Hypochondriacal paraphrenia	..	..	..	1	3	0	4
Phonemic paraphrenia	..	..	..	5	1	0	6
Fantastic paraphrenia	..	..	..	1	2	0	3
Incoherent paraphrenia	..	..	..	0	2	0	2
Phonemic confabulatory paraphrenia				0	0	1	1
Phonemic fantastic paraphrenia	..			1	0	0	1
Total	..	..	..	13	9	1	23

Recently Roth (1956) has used the term "late paraphrenia" to designate a group of senile paranoid states, but it is not clear whether or not he believes that this illness is schizophrenic. Since Mayer (1921) has showed that paraphrenia cannot be distinguished from paranoid schizophrenia it is unwise to use the term paraphrenia to designate an illness which is not schizophrenic. Late paraphrenia can also be confused with Bleuler's late schizophrenia. Thus it would appear that Roth's choice of term is unfortunate.

In view of the unsatisfactory nature of our knowledge of the incidence and form of schizophrenia occurring in the senium it was considered advisable to investigate a representative group of senile psychiatric patients. In mid-1958 information was obtained about all persons over the age of 60 and resident in the City of Edinburgh, who were admitted to psychiatric institutions in the year 1957. The institutions involved were one neurosis unit, two public mental hospitals, two private mental hospitals and four nursing homes. In 22 cases only the diagnosis of the admitting doctor could be obtained but in the remaining 242 cases the case notes were carefully studied and in many cases the patient was examined. The classification of those patients into different clinical groups is shown in Table III. The accuracy of this classification is doubtful

TABLE III

Clinical Classification of 264 Senile Psychiatric In-Patients Admitted from the City of Edinburgh in the Year 1957

Affective disorders	111
Schizophrenia	16
Senile dementia	50
Arteriosclerotic dementia ..	37
Confusional states	15
Miscellaneous organic states	7
Pre-senile dementia	6
Psychopathic personalities ..	6
Alcoholic addicts	8
Neurotics	4
Sexual perversion	2
Mental defect	1
Atypical facial pain	1
Total	264

since the period of follow-up varied from six to eighteen months. The criteria for the differentiation of arteriosclerotic dementia from senile dementia were those used by Roth (1955). Many workers doubt that it is possible to differentiate between those two groups of illness on clinical grounds (Müller, 1959) and the present author is of the opinion that it is difficult to do so and may often be impossible.

All cases in which marked paranoid symptoms occurred were designated "paranoid states" and subjected to special scrutiny. There were 41 such patients and they could easily be classified into four groups as shown in Table IV. The

TABLE IV
Senile Paranoid States in Edinburgh, 1957

Schizophrenia: Onset before 60	..	..	..	..	..	..	9	} 16
Onset after 60	..	..	..	..	..	..	7	
Paranoid depressions	..	..	..	..	..	..	..	6
Organic psychoses	..	..	..	..	..	..	..	16
Psychogenic reactions	..	..	..	..	..	..	..	3
Total	..	..	..	..	..	..	..	41

terms "schizophrenia" and "paranoid depression" are used here in accordance with the definitions given by the author in previous papers (Fish, 1959a, 1959b).

In the 16 cases diagnosed as schizophrenia the illness had probably begun before the age of 60 in nine cases. Thus the incidence of schizophrenia in the whole series was 6.0 per cent. and in 56.2 per cent. of the schizophrenics the illness had begun before the age of 60. In five patients the illness had begun before 50 years of age. In the other four patients with a probable onset in the sixth decade three could be classified as affect-laden and one as phonemic paraphrenia (Leonhard, 1957).

The seven cases where the illness began after the age of 60 will be referred to as senile schizophrenics from now on. The age of onset in this group ranged from 62 to 71 years with a mean age of 66.3 years. There were five females and two males. The duration of illness before admission ranged from one to eleven years with an average of 4.2 years. Two cases were re-admissions. The clinical pictures were variable but all cases could be classified according to the Leonhard scheme as is seen in Table V. Affect-laden paraphrenia was the commonest

TABLE V
Classification of Seven Senile Schizophrenics Found in a Series of 264 Senile Psychiatric Patients

Affect-laden paraphrenia	..	..	..	..	..	..	..	3
Phonemic paraphrenia	..	..	..	..	..	..	..	2
Hypochondriacal paraphrenia	..	..	..	..	..	..	..	1
Expansive paraphrenia	..	..	..	..	..	..	..	1

variety of schizophrenia but the clinical pictures within this subgroup may be very different (Leonhard, 1957) since the diagnostic feature is the presence of marked affect in association with the paranoid delusions. Thus in the three cases considered here, one had a circumscribed delusional psychosis which almost completely centred around her husband, one had many diverse non-systematized persecutory delusions which were associated with much affect and the third had an acute hallucinatory psychosis which settled down into an autistic state in which the patient actively avoided all personal contact and would not talk about herself or her symptoms.

At the time of the follow-up which was between six months and a year after admission, three senile schizophrenics had been discharged. One hypochondriacal paraphrenia who had been discharged was followed up by letter as her husband did not wish me to see her personally. He claimed she was very well and attributed this to the chlorpromazine which she was still taking. This is not very reliable information because the husband had minimized the severity of his wife's symptoms throughout the illness. One discharged phonemic paraphrenia could not be contacted because of his wife's depressive illness which might have been worsened by a home visit and enquiries about her husband's illness. However, there is now evidence from another relative that this patient has relapsed and it is likely that he will be re-admitted in the near future. The third discharged patient, an affect-laden paraphrenia, could not be contacted as the responsible relative did not answer the follow-up letter.

Roth (1956) has stressed the possible causal effect of physical and social isolation in "late paraphrenia". In the seven senile schizophrenias in the present series one was blind and lived alone, one had very poor vision and aortic incompetence and one lived alone but was physically fit. Four of the patients lived with their spouses and one lived with her son and daughter-in-law. Thus three of the seven senile schizophrenics had social and/or physical isolation.

In the affective group there were six patients with paranoid depressions. The ages of onset ranged from 61 to 80 years with a mean age of onset of 69.2 years. In four patients there appeared to have been an adequate provoking factor. In two cases this was worry about a close relative, in one it was the death of a close relative and in the fourth case a severe prolonged epistaxis which was severe enough to necessitate hospital admission. All six patients made a rapid recovery on receiving E.C.T., and were all discharged from hospital within six months of admission. The average length of stay in hospital was four months.

The sixteen organic paranoid states gave rise to no diagnostic difficulties. There was a clear disorientation for space and time in all cases. The distribution of the cases according to the causative illness is shown in Table VI. Six female

TABLE VI
Causes of Organic Senile Paranoid States

Toxic confusional state	..	..	..	..	..	..	..	..	4
Epilepsy	..	..	..	..	..	..	..	..	2
Arteriosclerotic and senile dementia	..	..	..	..	..	..	..	..	5
Uncertain origin	..	..	..	..	..	..	..	..	5

patients had a fairly well organized paranoid hallucinatory psychosis with obvious organic signs. The ages of these patients ranged from 79 to 85 years, with a mean of 81.3 years. In two of these cases death occurred three and eleven months after admission but unfortunately post-mortem examination was not carried out in either case. One patient deteriorated rapidly and within six months was utterly demented and bedridden. One patient was discharged from hospital within a few weeks of admission and her relatives did not answer the follow-up letter. Two patients developed a chronic confusional state with persecutory delusions and visual and auditory hallucinations. These patients were partially orientated during the day but became very confused at night. Thus it appears that some elderly patients about 80 years of age may develop an organic paranoid state which can become chronic. The exact nature of the

organic basis of this psychosis is not certain but the author hopes to investigate this problem further.

The three patients with psychogenic reactions could easily be differentiated from other paranoid states. They had all been awkward difficult people throughout their lives. One was a 61-year-old German-speaking Balt who came to Britain as a refugee. She became upset following the death of her mother and threatened to commit suicide. She was therefore certified and then became extremely paranoid about the certifying doctors and her sponsors. Her illness subsided when her discharge was arranged. The second patient was an 86-year-old woman, who had always been a rigid humourless person and given to complaining about her neighbours. For several months before admission she had accused her neighbours of making noises to annoy her but finally she became so abusive to the neighbours that she had to be certified. She settled down immediately following her admission and was discharged to an Edinburgh Corporation Old People's Home after six months. When I saw her after she had been in this home for five months, she was quite happy and contented, moderately well-orientated and the staff reported that she helped with the domestic work and helped other inmates to dress. The third patient was an 82-year-old woman who believed that her daughter-in-law had tried to poison her and had stolen money from her. When seen fifteen months after admission she was well orientated and quite content to stay in the old ladies' ward of a public mental hospital. According to her relations she had been drinking up to six quarter bottles of brandy in a day prior to her admission although the patient herself denied drinking much alcohol. This patient's illness was probably due to the combined effects of her previous abnormal personality, normal senile intellectual changes and excessive consumption of alcohol.

Although these last two patients have been called psychogenic reactions one cannot exclude the possibility that senile intellectual and emotional changes probably played a part in the development of the paranoid state. It is reasonable to suppose that normal senile changes might release a schizophrenic psychosis or might make a paranoid individual frankly psychotic. During my work at St. Nicholas' Hospital, Gosforth, I found one case history and one patient, which supported this view.

The patient, A.E.P., 82 years of age, was admitted as a certified patient to St. Nicholas Hospital on 10 January, 1956. She complained that strangers spied on her and looked through her bedroom windows when she was dressing. She said that her daughter and her son-in-law had conspired against her and tried to poison her. She also stated that her son-in-law had arranged for neighbours to smear paint on the walls and floor of her house. She was partly orientated for time and place, thus on 11 January, 1956 she said the date was 9 January, 1956 and the place was Newcastle Hospital. She had severe arthritis of the left hip and walked with great difficulty, her vision was very poor and she was slightly deaf. The patient was a widow who lived on her own because she refused to live with her only daughter. The daughter said that her mother had been a suspicious, cantankerous domineering woman all her life. Many years before when the patient's husband was alive, she had accused people of entering her bedroom and disturbing her possessions. In order to prevent this she had a Yale lock put on her bedroom door. She was her husband's second wife and for a long time she accused him, quite unjustly, of incestuous practices with the daughters of the first marriage.

During her stay in St. Nicholas Hospital she became more disorientated but persistently expressed persecutory delusions about her daughter. When I saw her again at St. Nicholas Hospital in May, 1958 she was utterly disorientated for time and place and refused to agree that she was in a mental hospital. She said she was about 90 years old. She claimed that her daughter had cut the sleeves off her blouse in order to bare her arms out of spite. She talked of her religious beliefs and became tearful. She resented her helpless physical state and was distressed by her failing sight saying, "What is going to happen to me when I go blind?" Within the limits of her physical disabilities she was able to look after herself, feed herself and make her wants known.

This patient was undoubtedly a paranoid personality. It would appear that under the influence of normal senile mental changes and a severe visual defect she had become psychotic.

The second patient, F.B., was a 79-year old woman, who was admitted to St. Nicholas Hospital as a certified patient on 5 May, 1938. Her daughter M.F.B., was admitted to St. Nicholas Hospital on 4 August, 1922 with schizophrenia and was one of a series of chronic schizophrenias investigated by me (Fish, 1958a), and has been classified as a phonemic paraphrenia. According to the relatives F.B. had only been ill a few months prior to admission. The certificate stated, "She has delusions of persecution imagining that attempts are made to poison her. She also talks about being annoyed by spirits." The admission note stated, "Very confused, disorientated, rambling in her talk and expressing delusions. She says her age is 81 this week or last week, that the year is 1889 and she was married in 1890. She says she is now in South Africa, her daughter is building a convent here; that they have cut out her tongue and every bit of food they bring her is poisoned and her stomach is burnt out." This patient finally died in St. Nicholas Hospital at the age of 94 on 15 December, 1952. In the course of the years she became blind and deaf but continued to have auditory hallucinations which from time to time led to outbursts of swearing. Despite the complete disorientation, she was not incontinent, could feed herself and could ask for a bed pan when necessary up until her final illness in 1952. She had a cerebral thrombosis on 6 November, 1952 and died on 15 December, 1952. No post-mortem examination was made.

Thus it would appear that this patient developed schizophrenia in which auditory hallucinations were the most prominent feature although hypochondriacal hallucinations were probably present at the onset. This psychosis was coloured by the normal senile mental changes and by her severe sensory defects. Although she was always disorientated she could make her wants known and feed herself 14 years after her admission. This makes it unlikely that she suffered from senile dementia.

DISCUSSION

The outstanding finding in this investigation is the difference between the incidence of schizophrenia in this series from that of other investigators. Thus Roth (1955) found an incidence of late paraphrenia of 9.9 per cent. and that in the majority of these patients the age of onset was over 60 years. Whereas in a series of 198 female senile patients Robertson and Mason Browne (1953) found an incidence 11.6 per cent. of cases of paraphrenia and schizophrenia, only three of whom (13 per cent.) had an age of onset at over 60 years. In the present series 6.0 per cent. of the senile patients were schizophrenic and in 43.8 per cent. of these patients the onset was after 60 years. If however the incidence of all functional paranoid states in the present series is estimated then this is 9.4 per cent. and in 72 per cent. of these cases the age of onset was over 60 years of age. Thus it could be argued that Roth's late paraphrenia corresponds to three of the author's subgroups of paranoid states. However the discrepancy between findings of Roth and the present author on the one hand and those of Robertson and Mason Browne on the other is not easy to account for except on the basis of the fact that private mental hospital facilities are more readily available in Edinburgh than elsewhere and the cases of senile schizophrenia would be more likely to be filtered off into the Craig House division of the Royal Edinburgh Hospital.

The only other large series of senile psychotic patients is that of Lechler (1950). Unfortunately this author did not discriminate between the patients with clinical pictures of functional psychoses who also had coarse brain disease from those who did not. In a series of 355 patients over the age of 65 years, who were admitted to the Heidelberg clinic between the years 1932-1948 he found thirty schizophrenias (8.4 per cent.). In eighteen of these patients there

was an age of onset over 65 years. If Lechler's criteria are applied to the present series then there were thirteen schizophrenics admitted when over the age of 65 and in nine the illness began after the age of 65. It is probable however that Lechler included patients in his schizophrenic group whom the present author would consider to be paranoid depressions. Thus Lechler found that a depressive mood was very characteristic of senile schizophrenia and that the illness was frequently provoked by severe psychic trauma.

Roth has suggested that there is a fairly characteristic clinical picture in late paraphrenia. This is not in keeping with the present author's findings. More recently Janzarik (1957) had studied a series of fifty senile schizophrenias and has classified them into five different groups, as seen in Table VII. Despite

TABLE VII
Classification of Fifty Senile Schizophrenias
(After Janzarik)

Acute delusional psychoses	..	..	..	..	..	..	..	..	6
Acute delusional psychoses with isolated auditory hallucinations	..	..							4
Chronic paranoid psychoses	..	..	..	..	..	..	..	..	3
Persecutory-hallucinatory psychoses		..	..	..	..	..	..	..	23
Hallucinatory psychoses	..	..	..	..	..	..	..	..	11
Catatonia	..	..	..	..	..	..	..	..	3
Total	..	..	..	..	..	..	..	..	50

differences in grouping both Janzarik and the present author appear to agree that there is no one typical clinical picture of senile schizophrenia. From the illustrative protocols of cases in Janzarik's first two groups it would appear that these two groups correspond to the present author's paranoid depressions.

SUMMARY

In a series of 264 senile psychiatric in-patients admitted from the City of Edinburgh in the year 1957, 41 patients with marked paranoid symptoms were found. Those paranoid states due to coarse brain disease could easily be differentiated from functional organic states which in their turn could be classified into schizophrenias, paranoid depressions and psychogenic reactions. A small group of very elderly patients with fairly well-organized organic paranoid states was found. The concept of late paraphrenia is considered to be doubtful. The term probably designates a heterogeneous group of non-organic paranoid states, only some of which are schizophrenic. Late paraphrenias which are obviously schizophrenic are considered to be best designated as senile paraphrenias. No distinctive clinical picture of schizophrenia was found in old age. The possibility that normal senile mental changes may produce a psychosis in a paranoid personality or may provoke schizophrenia is discussed.

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THE SYMPTOMATOLOGY OF MENTAL DISEASE AMONG REFUGEES IN NORWAY*

By

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I. INTRODUCTION

The Problem

IN an earlier investigation the author (1959) raised the question regarding whether a higher *incidence* of psychiatric disorders could be observed among refugees who remained in, or came to Norway after World War II. Through a personal investigation of all the (sixty) refugees who were admitted to Norwegian mental hospitals and psychiatric departments during the period 1 January, 1946–31 December, 1955, it has been possible to answer this question in the affirmative and without any shadow of doubt. The author could also show that the incidence of psychoses among refugees in Norway is, for all diagnoses, five times higher than could be expected when compared with a matched Norwegian population. For schizophrenia alone the incidence is less than five times higher, while for reactive psychoses it lies far above this number.

The next question to be answered was how far the *symptomatology* presented by the refugee patients differed from the symptomatology presented by a matched Norwegian patient material.

The basic material was composed of 95 refugee patients who during the course of the 10-year period from 1 January, 1946–31 December, 1955 had been treated in psychiatric departments in Norway. These 95 patients consisted of 60 psychotics (50 males and 10 females) and 35 neurotics (26 males and 9 females). The psychoses include 14 schizophrenias (all males), and 42 reactive psychoses (32 males and 10 females) and 4 organic reaction types. Among the neuroses we find 14 (12 males and 2 females) conversion states, the remainder were, on the whole, divided equally among all the other forms of neuroses.

Ninety-five patients do not offer a very large basic material and it is solely owing to the detailed psychiatric investigation to which the author was able to submit the patients, and to the exact knowledge he has of the control patients that he is able to consider it justifiable to publish the result of the investigation.

The Norwegian matched material was gathered in the following manner: for every refugee patient a corresponding patient was selected from the admission register of the psychiatric department of the Oslo University Hospital, that is to say, one who had the same diagnosis, who was admitted at the same time, that is on the same day, or one of the following days, as the refugee patient was either admitted to a psychiatric hospital or examined as an out-patient.

Symptoms which appear to be of special importance among refugee

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patients were persecutoric delusions, disturbances of consciousness, conversion symptoms and ideas of jealousy.

II. PSYCHODYNAMIC OBSERVATIONS

(a) *The Problem of Isolation*

Even a superficial consideration of refugee patients will result in the opinion that isolation must be of importance for the patients' mental health. In the present investigation, isolation is therefore subjected to a somewhat detailed examination.

The term *isolation* is used in very different meanings in psychiatric literature. Kraepelin (1899) described the "Verkehrspsychosen" with its subgroup "Verfolgungswahn der Schwerhörigen". He explains this paranoid reaction by a spiritual "Vereinsamung" and helplessness combined with simultaneous auditory illusions. This form is, according to Kolle (1931), not very frequent. He states in his survey of Kraepelin's 30,000 patients that "Verfolgungswahn der Schwerhörigen" was found in 12 males and 13 females only.

Houston and Royse (1954) carried out a clinical investigation of Kraepelin's problem and their material was composed of 40 deaf psychotics and 40 with normal hearing. They found 17 paranoiacs among the deaf patients as against 8 among those who could hear. Other investigations which should be mentioned in this connection were carried out by Faris (1934), Hyde and Kingsley (1944), Ødegård (1945), Fraser (1947), Sheldon (1948), Post (1951), Clausen and Kohn (1954) and Felix (1956).

Literature concerning psychoses occurring in connection with *isolation because of a total change of environment* has been of great importance for the present investigation. First and foremost should be mentioned Allers' (1920) account of acute psychotic conditions occurring among prisoners of war who could not communicate verbally with their surroundings because of difficulties of language. Allers calls this form of illness which has not been described previously, "Verfolgungswahn der sprachlich Isolierten". He is, however, of the opinion that here is a syndrome which can be compared dynamically with the psychoses of the deaf as described by Kraepelin.

The problems of *extreme isolation* as described by polar explorers, arctic winter dwellers, isolated seafarers, etc. have been the object of different experimental-psychiatric investigations. The pioneer work was done at the Institute of Psychology at McGill University, under the leadership of Hebb (Heron *et al.*, 1953; Bexton *et al.*, 1954) and at the National Institute of Mental Health in Bethesda, (Lilly, 1956).

It is interesting to note that both Lilly's and Hebb's experimental persons suffered lengthy after-effects following the experiments, with disturbances of the perception mechanisms. A series of illusions persisted for several hours, and it was also necessary for them to adjust themselves afresh to the "new" surroundings. These experiments seem to show that the mind of a person who is isolated will turn inwards and be projected beyond its own content and processes. The brain continues active in spite of the reduced frequency and intensity of impulses. In the later discussion the author will return to the importance these findings may have for a psychodynamic explanation of the refugee patients' psychoses.

Papers concerned with the importance of isolation for mental illnesses show thus that the meaning of the term varies greatly with every author.

However, this also proves that no psychodynamically convincing explanation has yet been offered for the pathogenetic importance of isolation.

Kraepelin's "Verfolgungswahn der Schwerhörigen" can, however, be explained by simple psychological observations. There is a lack of actual stimuli and at the same time the patient is troubled by auditory hallucinations. These are misunderstood by individuals predisposed to this reaction and a paranoid psychosis is started. A similar mechanism may also be thought to be present in those cases where the patients live in isolation, are growing old and so on, but do not change their national, social or cultural environment.

In all these cases a *lack* of stimuli is present. This lack of stimuli leads to a *feeling of insecurity* in the exposed individual who projects this feeling of insecurity upon his surroundings, thereby laying the foundation for the development of paranoid delusions.

The situation is quite different in the cases described by Allers. And even if Schneider's (1930) observations are correct, namely, that it is not only a question of changes of language but also of environment, this does not contribute to a deeper psychodynamic understanding of the paranoid conditions described here.

N. Cameron (1943, 1943a) has pointed out that the individual's adequate social behaviour is built up only through a continual interchange of experiences of one's own attitude to other persons, and through the modifications and corrections that this attitude is subjected to, through this very "continual interchange". However, the personality's constitutional traits play a decisive role. While one person can let an experience pass without reacting to it, another, through the same experience, will be spurred to a special activity (cf. also Langfeldt, *The Hypersensitive Mind*, 1951).

(b) *The Amount of Stimuli*

In the author's opinion, the isolation psychoses as described by Kraepelin, Faris and Houston, etc., cannot be compared psychodynamically with the psychoses described by Allers, Schneider, Knigge (1935) and others. While in the first cases it is a question of a *lack of stimuli*, perhaps accompanied by a misinterpretation of sensory impressions, the cause of the psychoses in a strange environment (be it either lingual, national, social, etc.) will be an abundance of, an "overflowing" of stimuli. The personality is literally flooded with outside impressions. These impressions will have a threatening effect on the individual who is threat-orientated. The motley multiplicity of these impressions which appeal to every sense and degree of experience will demand such great adaptability that individuals who are less well equipped intellectually or affectively will not be able to resist this flood of outside impressions: they will react pathologically to it.

The quantity of stimuli is so great that a "corrective and modifying effect" (Cameron) on an individual's behaviour cannot come into action. An "interchange" of experiences is out of the question in such a quantitatively oblique relationship as confronts a person when he lives isolated in a strange milieu. This will result in a feeling of insecurity towards the surroundings and environment as well as a projection of the insecurity on to the surroundings. This again results in a diminishing power of orientation, that is, the victim cannot settle down in the new surroundings, and *disorientation* and *confusion* develop beside the persecutory paranoid delusions. This will also explain in a natural way the various pictures of psychosis described by Kraepelin on one side and Allers on the other.

(c) Sociological Points of View

In sociology the terms "group" and "role-taking" occupy an important position. The individual's role in the group is on the whole clearly defined (Newcomb, 1952). The attachment to the group, that is to say, the acceptance of the role which each individual is tacitly expected to play, is considered to be decisive for the individual's adjustment (Simmons and Wolff, 1954). Weinberg (1952) states that it is only in the *groups* that the individual acquires knowledge of language, gestures, status, roles, aspirations, understanding of himself and others, in other words, that he becomes "socialized", acquires a "social relationship". It is not so much the verbal influence as the unconscious expectation of the others within the group which confronts the individual and which forms the symbols, meanings and behaviour patterns. The part played by a person in his group and the criticism of behaviour shown by the group are decisive for that person's social position.

For the development of personality, the degree of security that an individual can feel in his relationship to others is of great importance.

The "role-taking" in itself, that is the fact that certain attitudes are accepted, need not be thought about, are performed automatically as it were, is very important. It gives the individual security and saves him from mental strain. There can surely be no doubt in the assertion that the fact that one need not take up a position every moment, every day, again and again, towards one's surroundings, that one's behaviour, one's "ways" and conduct expectations and so on are ingrown, is of great importance for the liberation of mental energy for other purposes. The individual does not constantly receive new stimuli from his surroundings to which in one way or another, he must adjust himself. The majority of our everyday reactions occur without our reflecting over them. This mechanism in our psyche can easily be compared with the automatism which characterizes a part of our physiological existence. We walk, stop, move in traffic and so on, without thinking about the mechanism of our actions. A good car driver reacts "automatically" to all traffic obstacles without thinking that he must brake, change gear and so on.

If—instead of reacting mechanically—we were to let all stimuli into the brain, examine them carefully, consider the reactions and then finally perform them, our life would become considerably more difficult. This mechanizing, this automatism is a relieving and protective mechanism both with regard to mental and physical reactions.

By a transplantation to a completely new environment, be it lingual or not, the hitherto acquired mechanism and automatism become useless. Such a simple thing as how to answer a greeting becomes a problem which must be consciously solved. A short journey by tramcar which can be undertaken in one's customary environment without reflecting over it, and while one simultaneously is occupied with other matters, becomes, in strange surroundings, a problem which must be solved from detail to detail. Much more serious than this "technical" uncertainty is the insecurity one feels toward people one meets and new social situations which confront one. The "accepted role" from the old, familiar group does not help, one must, at the start, improvise, later learn new roles, and one never knows how the new individual or group will react to the improvisation. (The feeling of security in the old group was composed of this very fact that not only did one know how to react oneself, but also how the other members of the group would react to one's actions and how one's group expected one to behave (Kahn and Richter, 1939).)

This continual insecurity results in an increase in the number of situations which must be taken into consideration, a course planned and a decision reached. In other words, not only is the number of stimuli which affects the individual redoubled many times, but also the decisions he must make. If the individual is equipped with sufficient resources he will—if the conditions in other respects are not too bad—be capable of adjusting himself to what is expected of him, and “grow” into the new roles in the way the new groups count upon.

If the group formations one meets are not fundamentally different from the previous ones, the situation is less complicated. Skilled workers, such as car mechanics, tailors and so on, who know the work processes of their trades and the demands made of them at the place of work, which to a certain extent resembles the old one, will “settle down” more easily, firstly at the workshop and later also in the other new surroundings. Their acquired “role taking” does not need to be changed fundamentally in all respects of their life. The situation is far more difficult where there is no relationship between the old group formations and the new. In these cases new “roles” have to be learned in *all* respects, *all* new stimuli must be revised, and since the number of these seems overwhelming for less elastic personalities—either intellectually or emotionally poorly equipped persons—one is then confronted with the situation previously described as a “flood of stimuli”, a situation with which a relatively primitive individual will not be able to cope. The result will then easily be a pathological reaction, which in its most primitive form is a “complete breakdown”.

From a *neurophysiological* point of view, Grey Walter (1953) describes the phenomenon as follows: “. . . Difficulties of communication increase with the number of units, if at the same time *the variety of signals also increases, the whole organism will soon become useless and break down.*” Psychiatrically speaking a “breakdown” such as this will be mainly characterized by perplexity and confusion. These states of illness occur quite often in our material of refugee patients.

This explanation appears to be, to a certain extent, in opposition to the importance of extreme isolation (which we have discussed previously in this paper) and to the experimental investigations which have been carried out in this field. The contradiction is, however, only apparent, as the first and immediate feeling in a strange milieu will usually be this particular feeling of loneliness and rejection. The manifold external impressions do not create any feeling of solidarity, of an understanding of the situation or of the inner meaning of the impressions, and first and foremost, no understanding of the individual's position in the whole of this unknown and overwhelming system. It is precisely this lack of ability to receive, to understand, to develop and to react to the surroundings which causes this apparent but none the less very familiar paradox of feeling *isolated*, of being totally alone as Lilly's experimental persons in the water tank, while one is actually surrounded by masses of talking, laughing, active fellow-beings, be it on Karl Johan Street in Oslo, on Piccadilly Circus in London, or on Fifth Avenue, New York.

We have thus two different mechanisms which cause psychotic reactions: the primitive, *unabsorbed* feeling of being overwhelmed by outside impressions and stimuli which cannot be digested, and thus lead to confusion, and in addition to this the reaction to the feeling of loneliness which is first and foremost marked by insecurity. The feeling of “not belonging”, of not being able to take a role in some form or other, of not knowing what is expected of one, add insecurity to isolation.

The feeling of isolation is intensified by the need of contact. Doubtlessly this varies strongly from individual to individual, and, in the same way, the means of its satisfaction. In a human material as the refugee patients, the need of contact will be great, urgent, and the lack of its satisfaction will be hurting and increase the intersychical insecurity. The latter will, in turn, be projected on to the surroundings and be the source of paranoid reactions. With reference to the above-mentioned theory we may expect to find, among refugee patients, a number of psychotics with both persecutory paranoid delusions and confusional states.

III. THE PERSECUTORY-PARANOID REACTIONS

Villars Lunn (1953) defines paranoid states as being characterized by the presence of delusions and adds that delusions may appear in the course of practically every known form of mental illness. The paranoid symptom has thus, in itself, no special diagnostical value, the persecutory traits, however, are worth consideration.

It would therefore perhaps be more correct to ignore the numerous discussions on the division of the paranoid syndromes and concentrate here on an attempt to explain briefly the persecutory-paranoid experience. A line can be drawn from Wimmer (1902), over Bleuler (1906) to Kretschmer (1927, 1950) which attempts to explain the paranoid experience as an interplay between the projection personality's sthenic and asthenic components or "extremes", and a shameful "key experience" which cannot be reconciled to the individual's picture of himself, that is with his own personality consciousness. Freud and the psychoanalytical school (1924) have attempted to explain the different paranoid illusions from the viewpoint of homosexual complications with negative transformation. Macalpine and Hunter (1953) criticize this explanation strongly, and they take it up again and revise in detail and critically Freud's "Schreber-case", and base their opinion on the grounds that projection of unconscious homosexuality in spite of the fact that it may certainly have played a part in the symptomatology, cannot be considered as the cause of Schreber's psychosis, neither from a phenomenological nor from an aetiological point of view. Miller's (1941) paper should also be mentioned in connection with this. He thinks that he can show 12 cases answering to Freud's conception by a detailed and precise examination of 400 paranoid patients while he found many different psychological explanations for all the other paranoid cases.

Hodel's work (1954) is also of interest for our investigation. He reports a high incidence of paranoid conditions among Filipinos in Hawai, but does not enlarge on the psychogenesis. We would also mention Adeoye Lambo's (1955) work concerning the importance of cultural factors for paranoid psychoses in a negro tribe in West Africa, where persecutory delusions dominated the picture.

After this very brief survey, we turn our attention once more to our own patients. Among the 60 psychoses we find paranoid symptoms in 52 cases (44 males and 8 females), that is, only 8 patients did not have paranoid symptoms. Among 60 matched Norwegian psychotic patients we found only 28 cases with paranoid symptoms.

The distribution of the *persecutory* paranoid symptoms is even more remarkable. While 9 "refugee schizophrenias" have persecutory paranoid ideas, only 3 Norwegian schizophrenic patients showed corresponding persecutory delusions. Far more remarkable is the difference we find in the 42

reactive psychoses. Here we find 22 with persecutory delusions among the refugees and only 3 among the Norwegian controls. The finding of 2 persecutory paranoid patients among 4 patients with organogenic mental illnesses completes the picture.

The material presented here shows with desirable clarity that the paranoid syndrome with persecutory delusions is far more frequent among refugee patients than in a corresponding "matched" Norwegian material.

When we have contended earlier in this paper that the refugees' paranoid delusions are caused by their social isolation and their consequent insecurity, this does not imply that isolation is considered the pathogenetically *sole* decisive factor. However, the significance of this factor appears to be so predominant in our material that it is of importance to emphasize it. We will recall Hebb's and Lilly's isolation experiments and the conclusions drawn from them, namely, that an isolated person's psyche will turn inwards and project itself beyond its own thought content and processes. This occurs as the author has attempted to show, in other forms of isolation also (that is, not only in extreme experimental cases), for example in a community where a deficient exchange of experiences between the isolated individual and the overwhelming surroundings leads to misinterpretations, projections and paranoid thinking and reactions. A continued lack of criticism will result in a development of the paranoid picture.

The abnormally high incidence of the persecutory form of delusions is easily explained when one considers the patients' backgrounds. The majority have grown up in an atmosphere of national discord and mutual mistrust, they have spent the years of war in abject misery, completely at the mercy of guards' arbitrary treatment. After the war, many have lived for years in D.P. camps, this time dependent on I.R.O. officers, and different institutions. Even if the vent of aggression was not fatal in its literary sense here, it is obvious that it could result in (and actually did so) a serious reduction in the chances of final emigration. During their stay in Norway the patients are still further dominated by a whole series of factors which underline their dependency on authorities and institutions, and which place them in situations with which they cannot cope and to which they must needs feel themselves to be "delivered" as during their camp existence. Their mind is full of repressed aggression and hate towards their surroundings. It is incompatible with their social position, with the accepted norms, and also in fact with their conscious ego, to give vent to this aggression. In conflict situations or in other situations which exceed their psychic stability this hate is then projected towards their surroundings and results in persecutory delusions.

Besides this rather "indirect" pathogenesis for persecutory delusions, the more "direct" one should also be taken into consideration. This has its origin in the political situation, with its insecurity, with the possible actual persecutions, "shadowing" and so on. Persons who are disposed to such a reaction will easily ascribe relatively peripheral happenings to themselves and thus slide into persecutory delusions. In the same way, we see that persons who have made some mistake or other, concrete or only imaginary (and who have become used to all errors being punished severely), will expect serious reaction from their surroundings. The anticipatory anxiety will manifest itself in persecutory delusions. Furthermore, the patients will also react with persecutory delusions, either when they are reprimanded by their surroundings or, because of an inferiority complex, founded on reality or imagination, when they have experienced or expect reproof or disdain from their surroundings.

It would appear then, that the *individual's feeling of insecurity* is a common trait in the genesis of the paranoid delusions of different grades, *the trait that instils the individual with doubt regarding his relationship to his surroundings and which, with the help of projection, leads to the delusion that the surroundings are hostile to the individual.*

The following case histories of persecutory delusions attempt to shed light on the above-mentioned statements.

(a) *Schizophrenias*

Example 1. (Case 59): The patient was a Polish, unmarried man, a Roman Catholic, born in 1922. His father's fate was uncertain (he is perhaps living in Siberia), his mother is alive. He had been only to an elementary school and had had no further training. He came to Norway as a forced labourer in 1944. After the liberation he had many irregular employments and went eventually to sea in 1950. In the autumn of 1952, while on board a Norwegian ship, he started to notice that he was being spied upon. He could not stand it and left the ship in a Norwegian harbour. Here the situation deteriorated even more. Everyone was against him, and he was afraid of being killed, "they" had planned to kill him. In his desperation he sought protection at a public office telling the officials that murderers were after him. It was obvious that he was insane and he was delivered to a mental hospital through the usual channels. When hospitalized he attempted to escape, still being afraid of getting killed. Besides persecutory delusions, he suffered from ideas of influence, feelings of passivity and hallucinations. Neither E.C.T., insulin coma therapy nor ataraxies affected his disorder.

Followed up in 1956: the symptomatology remained unchanged.

Diagnosis: schizophrenia (paranoid type).

Example 2. (Case 33): The patient was a Polish, unmarried man, born in 1917. Both parents were dead. He had only had incomplete schooling and worked later as a farm labourer. He came to Norway during the war. After the liberation he proved to be a steady and good worker, and was in regular employment. However, he did not seek contacts, lived isolated, was rather dull and introvert. Some time before hospitalization he had received a letter from IRO, questioning him about his home town. After this "event" he became anxious and depressed. Once he had seen Jesus in dreams, thought therefore that he was to die soon, to be deported to Siberia and killed. He noticed that he was being spied upon, and went therefore to the police and complained that he was being persecuted, accused of spying and sabotage. He was sent to a doctor and submitted to treatment, but refused to take medicine which he thought was poison. He was convinced that the doctor was trying to get rid of him. After some time he had to be admitted to a mental hospital. Here he suffered from further persecutory delusions, massive hallucinations, both visual and auditory, feelings of passivity, and ideas of influence. Intellectually he was possibly slightly below average. There was a steady deterioration. In spite of E.C.T. and insulin coma treatment he became aggressive and insecure, and had to be treated in the maximum security ward.

Followed up in 1955 without attaining contact.

Diagnosis: schizophrenia (paranoid type).

In all the cases of schizophrenia it appears very clearly that the persecutory delusions introduce the actual manifest picture of the disorder. It may also be considered fairly certain that, in all probability, the schizophrenic *disposition* existed before it became manifest, when we take into consideration both the development of the above-mentioned case histories and common psychiatric experience. The latent schizophrenic patient is probably the individual who is most troubled by inner insecurity. The feeling of catastrophe which is so often a schizophrenic's dominating symptom, speaks for itself. This prevailing lack of security because of deep changes in the personality's ego consciousness, will, in the majority of cases, lead to projection and paranoid delusions. It can also be understood that the personality and politically insecure social situation colours the psychosis. In some cases, as for example in the last mentioned, a relatively unimportant happening, misinterpreted by the patient, is sufficient to start the latent process. This "relatively unimportant" happening has, however, touched on the patient's central problem, his feeling of insecurity, and the paranoid development is set going. In both the cases described here, it is clear,

however, that the persecutory-paranoid delusions are only a pathoplastic feature in the picture of the disorder. In the course of the schizophrenic process, they become of less importance to the patient and consequently are less to the fore in the picture of the disorder. The emotional flattening also contributes to the fact that the patient is not so preoccupied with his persecutory delusions, even though they are still present, a fact which could be shown clearly in many case-histories (not referred to here).

In summing up we may assert that the persecutory paranoid symptom appears in schizophrenic patients as a pathoplastic feature, based on the same psychic mechanisms as previously mentioned. It can often introduce the manifestation stage of the psychosis, a fact which may at the beginning often cause difficulties in the differential diagnosis. The other symptoms appear later in the course of the disorder, among them marked splitting phenomena, and give the illness its characteristic traits and course.

(b) *Reactive Psychoses*

We have attempted below to classify the 22 cases of *reactive psychoses with persecutory paranoid delusions* into several subgroups, according to the external conditions which may be thought to have contributed to the development of the said syndrome. The first group consists of patients in whom a feeling of personal inferiority, organ inferiority, a feeling of inferiority towards a Norwegian "friend" or wife has marked the development of the disorder. For example:

Example 3. (Case 32): The patient was a Yugoslav, Greek orthodox by religion, a married man born in 1921. Both parents living. He grew up as an only child under disharmonious home conditions. Both parents were unfaithful and the patient was always considered to be a "difficult" child. He went to primary school for seven years and later became a mechanical apprentice. During the war he was in the Yugoslavian Navy, and was made prisoner of war by the Germans. Later on he was put to forced labour and came eventually to a Gestapo prison because of an attempt to escape. He attempted suicide in prison (by stabbing himself in the region of the heart), and later on developed pericardial adhesions following empyema and purulent pericarditis. He came to Norway just before the end of the war. He got married here but the marriage turned out to be a failure with continual scenes, reciprocal accusations and insults when the patient's origin was a favourite "topic of conversation" (Balkan bandit and the like). Gradually he lost his health, and serious hysteric symptoms of conversion appeared, which in turn led to hospitalization in a psychiatric hospital. Later on he developed persecution delusions, thought he was going to be killed, asked for police protection, begged them not to shoot him at once and so on. A gradual clearing up occurred after E.C.T. during the stay in hospital.

Followed up in 1956: the patient continued to be preoccupied with conversional complaints, and the marriage situation showed no improvement.

Diagnosis: psychosis reactiva (paranoid form).

The next example shows a persecutory forming of the delusions because of organic inferiority (blindness).

Example 4. (Case 6): The patient was a Polish Ukrainian, Greek Orthodox, a married man, born 1910. Conditions in his home were unfavourable. After primary school he was employed in casual labour, later on did forced labour in Germany and became blind in 1943 after drinking methylated spirits. After the war he married in a D.P. camp and came to Norway in the "blind transport". He found employment fairly soon. When the wife suffered a puerperal psychosis the family was temporarily broken up. The patient could not stand the strain. He became gradually apathetic, was afraid of being poisoned, toxicophobic, suffered from persecutory delusions. However, he improved fairly quickly under hospital treatment, but his persecutory delusions continued for some time after his discharge. During further interviews it appeared that his paranoid ideas started in connection with a female help he had had while his wife was ill. He thought that he was suspected of making advances to her, later the paranoid delusions increased, everyone persecuted him because he was a "blind refugee".

Followed up in 1956: good remission, but little catamnestic understanding of his delusions.

Diagnosis: psychosis reactiva (paranoid form).

This group of patients with persecutory delusions based—to a certain extent—on feelings of inferiority which increase their insecurity—includes naturally some Jewish patients. Here the experiences of war because of “innate inferiority” are still so vivid that they form an insuperable culture ground for persecutory delusions.

Example 5. (Case 22): The patient was a Polish Jew, born in 1926, and a married man. His parents and all his siblings were killed in concentration camps. The patient himself was arrested just after completing his primary education. After the liberation he suffered from tuberculosis and spent the time until 1952 in various sanatoriums with some D.P. camp internments during the “healthy” intervals. In 1950 he got married to a Sudetan girl and two years later was accepted in a “hard-core” transport to Norway. After arrival, the wife was then pregnant, he was placed alone in a small town, while his wife awaited her confinement in a home. He felt intensely isolated. “Well-meaning” people took care of him and suggested, among other things, that he should have the expected child christened so as to be a “proper Norwegian”. He became suspicious, developed, gradually, massive paranoid delusions, felt “opposed” and persecuted, and thought he was being poisoned. He was also afraid of being gassed and so on. On admission to the psychiatric department he was afraid, unhappy, perplexed, unclear, confused, and hallucinated. Remission after E.C.T.

Followed up in 1956: the patient was then well adjusted to his employment, the matrimonial conditions were good, and there were no remaining symptoms.

Diagnosis: psychosis reactiva (paranoid amentic form).

We can also freely include certain other patients in this group, namely, those whose political and national attitude during the war was uncertain, or not acceptable to the majority of refugees after the war. The following is a typical example:

Example 6. (Case 54): The patient was Russian; Greek Orthodox, a married man, born in 1905. Both his parents were dead, there was no known tainting in the family, three siblings were still alive and healthy. The information he gave personally was somewhat contradictory, but it appears to be quite certain that he was taken prisoner by the Germans during the war, and in an internment camp agreed to become a “Wlassow” soldier (1942 and 1943). He came illegally to Norway, and after long deliberation was granted residence permit. He showed no occupational adjustment, considered himself an “officer”, and a “scientist”, would not do ordinary work, but was willing to accept poor relief. From 1952 he suffered from massive persecutory delusions, thought that he was persecuted by “international terrorists”, that he would be poisoned in restaurants by “capitalistic groups”, “Polish Jews and GPU”. Occasionally he had anxiety paroxysms because “he had just eaten some poison”. He was admitted to hospital but showed only moderate improvement after E.C.T.

Followed up in 1956: the patient continued to be persecutory paranoid with no understanding of the disorder, and was unable to adjust himself.

Diagnosis: psychosis reactiva (paranoid picture).

In addition to this group we also have those patients whose social isolation and the resulting insecurity are obviously predominant, as in the following example:

Example 7. (Case 41): The patient was a Pole, a Roman Catholic, single man, born in 1926. His mother and one sister were dead, the father and 2 siblings were still alive in Poland. There was no known tainting in the family, the home conditions were modest, and he had had 6 years primary school education only. The patient was taken for forced labour to Norway in April, 1943. After the liberation he was sent to an aliens camp, and later worked as a lumberer and farm labourer. In 1953 he became an industrial worker, and was well adjusted. In connection with a political conflict at the workshop, he thought he was under suspicion, heard people talking about him everywhere, and thought that they demanded that he should be shot. He sought police protection, dare not sleep and had to keep watch. He was admitted to hospital with massive, persecutory delusions, which included the hospital staff. The patient reacted badly to E.C.T., but better to insulin coma treatment. He was intellectually far below average.

Followed up in 1956: the patient had then had a relapse and was again hospitalized.

Diagnosis: psychosis reactiva (paranoid picture in intellectually inferior person).

The re-examination of the case histories shows that the persecutory paranoid syndrome is, in nearly all cases, an expression of the patients' lack of security, with a projection of their insecurity towards the community. In addition to the constitutional source, the reason for this insecurity may be found in many different fields, and is intimately connected with the refugee way of life, and the manifold and varied problems this offers, including the patients' past before they were accepted as immigrants.

Parenthetically we would also draw attention to the fact that three of the persecutory paranoid patients were blind. In literature we often find discussions (see, among others, Houston (1954)) about the fact that *deaf* patients so often become paranoid, whilst this symptom is very rare among the blind. Our investigations show that in a group of only 35 blind refugees, there were three psychotics and all of these suffered from persecutory delusions. It is therefore reasonable to assume that the low incidence of persecutory delusions in blind persons as described above is a consequence of the community's more accepting and understanding attitude to blind people, whilst deaf persons, because of the slightly comical quality which is often connected with deafness, will feel more in opposition to their surroundings. With all the reservation due to such a small material, one can conclude that the blind who do not feel the sympathy of the milieu, and who, on the contrary, are filled with an aggressive attitude, or who are under the impression that their blindness is a serious drawback with regard to achieving the necessary contact with their new surroundings, will also possibly react in a paranoid way.

IV. DISTURBANCE OF CONSCIOUSNESS

The next syndrome to be investigated more closely was the *disturbances of consciousness*. The classification and psychogenesis of these have been considered by (among others) Jaspers (1920), Jahrreiss (1928), Strømgren (1945) and Rosenfeld (1950). Strømgren was able to show that a change in the patient's *object-consciousness* is apt to lead to disturbances in the form of clouding (vagueness) while the change in the *personality-consciousness* is the reason for paranoid reactions. In our material there was an accumulation of disturbances of consciousness which took the form of *confusional states*.

In the 42 reactive "refugee psychoses" we found the above-mentioned conditions in 14 cases, but only 1 in the corresponding Norwegian patients. There was an equal number of patients of both sexes, this is—relatively—a predominance of females (7 out of 10 as against 7 out of 32). It should be considered important for the present material that more than half of all the confusional states occurred during the first year after the refugees' arrival in Norway. A few brief case-histories will show the genus and problem in our material:

Example 8. (Case 8): The patient was a Ukrainian, a Greek Catholic, married? man, born in 1919. His story was at one time very much to the fore in the headlines of the Press as the sensation it in fact was. The patient had escaped from a German prison camp in 1944 and remained in hiding until 1946 without being aware of the fact that the war was over. He slept in barns, ate pig's food and whatever else he could "find". When he was found he was starving and very exhausted. He was first admitted to a medical department, but soon showed signs of persecutory delusions. He imagined that he was surrounded by the police and that he was suspected of being a Nazi. He gradually developed increasing restlessness and confusion. He was admitted to a mental hospital and showed a complete clearing up after E.C.T. After his discharge from hospital he worked as a dairy man with varying degrees of adjustment.

Follow up in 1957: the patient had been in regular employment during the last three years. There were no psychotic symptoms. There was an amnesia with regard to the psychotic period. He gave the impression of being intellectually below par.

Diagnosis: reactive psychosis with confusion and paranoid delusions in a primitive type of person.

In the case of this patient who was suddenly transferred from the existence of a fugitive where he thought his life was in constant danger, to a modern hospital with doctors, nurses and, moreover, journalists, photographers and other people and conditions which he could not understand, it will easily be understood and obvious that the flood of outside impressions is the reason for the resulting confusional condition.

Example 9. (Case 27): The patient was a Polish, Roman Catholic, unmarried man, born in 1903. His father was a crofter: there was no known tainting in the family. The patient was the eldest of 3 siblings. He did not know whether his parents and siblings were alive or not. His primary school education had not been completed, he was the worst pupil in the class, later on he just stayed at home. During the war he was a forced labourer in Germany, became later a farm hand and lived in D.P. camps. He came to Norway as a "skilled worker", and was to start working on a farm. He very soon began to act strangely, talked to himself, and one day he disappeared and returned without being able to account for his actions. He also started to walk along the roads, shouting loudly. His employer tried to keep him however, and brought him into contact with other Poles, but without any success. The patient was finally admitted to a psychiatric hospital. He was then hallucinated, confused with persecutory-paranoid delusions. He thought he was to be burned, killed, was "kaput", destroyed. He became clearer under routine treatment, but proved to be well below average in intelligence, and he had little or no understanding of his situation. He was once more placed under the care of a farmer, but with the same result, that is to say, a renewed exacerbation of a paranoid psychosis. This time, however, no confusion occurred, but the course was otherwise identical. Later private care was tried.

Followed up in 1956: the patient showed no change.

Diagnosis: oligophrenic psychopath with psychotic exacerbations of amental and persecutoric nature.

In this case it seems quite obvious that the transfer of the patient to the new surroundings with all the unfamiliar impressions was too much for this primitive person. Although he had, on the whole, the same sort of work he had had all through his life, the fact that for the first time in his life and in strange surroundings, he had to stand quite alone, was too much for him. The quantity of new stimuli was too overwhelming. It is of importance to emphasize, in this connection, that the contents of his hallucinations consisted of either persecutory delusions or of illusions of being with his own family, hearing his mother's voice and so on.

The following case history shows another aspect of the same problem:

Example 10. (Case 57): A Polish, Roman Catholic, married woman, born in 1906. She came from very humble circumstances. Her schooling had been negligible, and had lasted for two years only. She was put to forced labour in Germany with her husband, and two of her children died there. She was completely dependent on her husband, extremely primitive, quite devoid of any personal opinion. Shortly after their arrival in Norway (1952) the husband's old tuberculosis reappeared and he died. After this, the patient broke down completely, became confused, restless and deeply depressed. She was treated with E.C.T., but relapsed shortly after. She died a year after her husband, extremely disconsolate.

Diagnosis: psychosis reactiva (amental, depressive picture).

Through her husband's death, this patient experienced a complete breakdown of her whole world, and was in no way fitted to build it up again. It was far beyond her ability and potentialities, to settle down in a strange country among strangers only. The breakdown was so complete that all areas of consciousness were irreparably affected because of the patient's lack of inner

resources. In its very tragedy, this case is an illustrative example of the importance of the premorbid personality for reactions to psychic trauma and for the further course of these psychotic reactions.

The other female patients with confusional states are represented best by the following example:

Example 11. (Case 60): The patient was a Hungarian, Roman Catholic, married woman, born in 1930. She came from a land labourers' home, where the conditions were very poor. She had been to primary school and was very dissatisfied with her working life. She fled to Austria in 1948, solely in order to earn more money. She continued to feel dissatisfied. In 1950, she married a blind Russian who was 10 years her senior, and whom she had known for a few weeks only. She had one child, twice abortus provocatus. The matrimonial conditions were bad, there were continual affective outbursts, serious delusions of jealousy and accusations. She came to Norway in 1952, and shortly after suffered from "very bad attacks of pain in her whole body", darting pains in her head. She was admitted to a surgical department, and wanted to be operated on, but no indication for this was found. She became very restless, had attacks of fainting and outbursts of uncontrolled rage. E.C.T. had temporary effect only. She was aggressive with constant affective outbursts, unclear and confused, and showed hysteriform characteristics. She felt that she was not sufficiently appreciated, and that she was persecuted by the doctors, nurses and "Norwegians on the whole". "Nobody wanted to help her, her husband was unfaithful, everybody wanted to destroy her, harm her, poison her". Her husband insisted on her discharge from hospital contrary to the advice of the senior physician. Later, her hysterical attacks continued with sessions of screaming and accusations such as those mentioned above. The whole stay in Norway had been "pure misery".

Followed up in 1956: the patient showed an extremely paranoid attitude both to the investigator and to all organized help. She was projective, "it was only the others' fault that she didn't get any work. She had been brought to Norway in order to be destroyed" etc.

Diagnosis: psychopathia, labile affective with psychotic exacerbation.

In the patients in this group we find a confirmation of Strømngren's (1945) opinion that people who use hysteroid mechanisms have a very sensitive object consciousness and that trauma which for others appear insignificant are capable of disturbing these individuals' labile balance and produce storms of affect which again result in new attempts at suppression by mean of splitting consciousness, vague states and delirious conditions.

The typical case-histories reported here show that disturbances of consciousness of confusional character appear in the material presented here mostly in patients with either labile psyche (hysteroid character) or with an intellect somewhat below par. Especially these latter persons are not able to adjust themselves to all the impressions and stimuli brought about by the new surroundings. The patients' lack of a feeling of security and the projection of this insufficiency result in paranoid illusions while the flood of stimuli leads to a failure of the basic ability of adjustment and thereby to a "breakdown of the personality" and to confusional states.

In order to avoid any misunderstanding the author wishes to emphasize that the mechanism which gives rise to disturbances of consciousness such as he has mentioned here in no way claims to be the explanation of all cases of this psychopathological process. He has merely attempted to prove that it can also come about in this manner. The life of the human soul is so complicated that it would be naïve to search for a one-sided explanation of a definite change in it.

V. CONVERSION SYMPTOMS

The symptoms which quantitatively follow those mentioned above are complaints over somatic disorders. Tyhurst (1951), Pfister-Ammende (1955) and Bibering (1951) have made similar discoveries.

Somatic reactions and the forming of conversion symptoms are no doubt

greatly dependent on both the patient's constitution and on his outer circumstances. The fact that these reactions are not brought about by "extreme situations" such as actual danger of death, shows that they are determined by the situation. Kral's account from Teresienstadt is of interest here. The author would, at this point, like to add a personal and rather illustrative observation. In Auschwitz an annexe camp was formed in connection with a FLAK-factory. During the first few weeks the prisoners had very little to do because the factory was not yet in running order. The atmosphere was also slightly more peaceful than under normal concentration camp circumstances, the whole business was marked by beginner difficulties, and the work in the factory was the centre of everybody's interest, instead of terror, disciplinary drill and the usual forms of ill-treatment of prisoners. The author was camp doctor and had during this period as many as 50 prisoners per day who consulted him for very varied and often very superficial somatic ailments and symptoms which were difficult to account for by an ordinary clinical examination. Once this "idyllic" period was over and an adequate number of German Capos were installed in the camp, and after the normal concentration camp atmosphere of a 12-hour working day, followed by disciplinary drill, lengthy roll-calls and so on was established, all these "patients" disappeared and were replaced by those one usually saw, namely, those with starvation oedema, phlegmones after wounds, teeth that had been knocked out, broken jaw-bones, fractured ribs and the like. (The author saw only *one* patient who although fully aware of the fate in store for him, preferred to die in the gas chamber because of a hysteriform paralysis of a leg, rather than "give up" his neurosis.)

With regard to *nomenclature* there never has been a united conception of the conversion symptoms. Jaspers (1953) writes quite simply: "Die Hauptmasse dieser somatischen Störungen nennt man Organneurosen". Strecker, Ebaugh and Ewalt, in the 5th edition of their text book (1940) refer to "conversion hysteria" only, while in the 7th edition (1951) the somatic reactions are divided into "conversion hysteria", "hypochondriasis" and "somatization reactions". The nomenclature which is accepted by the American Psychiatric Association distinguishes between "psychophysiologic autonomic and visceral reactions" and "conversion reactions". W.H.O.'s nomenclature discriminates between neurotic hysterical reactions and neurotic reactions with somatic symptoms from the heart, the digestive system and other organs. The Norwegian nomenclature which was proposed recently follows, on the whole, the international one, but it has a few more sub-divisions.

As may be seen from the above, a great deal more work is needed before psychiatrists can agree on nomenclature, and, what is perhaps even more important, on a commonly accepted meaning of the terms.

Under the heading of the symptom discussed here are included all those patients who during their illness complained of somatic disorders to so great a degree that these complaints were not only the reason for closer investigation but also coloured the picture of the illness.

The symptom occurred among the refugee patients in 45 cases, that is, in almost half of all the patients. Compared with the "Norwegian material" where the same symptoms appeared in only 19 cases, this difference shows, statistically, a valid result.

Of the 26 male patients with neurosis, 21 had conversion symptoms, while 8 of 9 neurotic female patients had these symptoms. Among the psychotics there were 10 out of 50 men and 5 out of 10 women. In the Norwegian material the totals were, respectively, 9 and 3 for the neurosis and 5 and 2 for the

psychoses. The totals show clearly that conversion symptoms are extremely common among the refugees. Patients suffering from neuroses have somatic complaints in more than 80 per cent. of the cases.

If we attempt to find an explanation for the frequent appearance of somatic symptoms, it would be natural, as a starting point, to recall the total absence of such symptoms in "extreme situations". The first conclusion to be drawn from the appearance of these symptoms is the fact that refugees do *not* regard life in their new surroundings as a really perilous situation. This negative explanation does not, however, clarify adequately the remarkably high incidence.

Somatizing symptoms are, in themselves, not actually rare, and this applies both with regard to the neuroses and the psychoses. It is also well known that the schizophrenias can begin with relatively long periods when somatic complaints dominate the picture. It has been previously shown that, in this material, there is a comparative predominance of patients from the lower socio-economic classes, with a very low average school education. Primitive individuals will be inclined to react with somatizing symptoms rather than with more "complicated" psychoneurotic mechanisms. A part of the "somatic predominance" may therefore be attributed to "the factors of primitiveness". We are under the impression, however, that this does not sufficiently explain the very remarkable difference. Neither does Tyhurst's statement that the refugees' self-absorption produces somatic symptoms offer a fully satisfactory explanation of why this self-absorption should lead to somatic symptoms only, and not to psychic symptoms also. In *favour* of this opinion is the fact that the extensive physical ill-treatment the refugees have suffered concentrates their pre-occupation with self on somatic sensations. But this explanation can hardly be considered satisfactory. The experience one has with former concentration camp prisoners who have returned to *their own country* shows that the prisoners certainly had diffuse neurasthenic symptoms at the start and that these often persisted for several years. However, when these patients were admitted to psychiatric wards, their main symptoms were not somatic complaints, but rather anxiety symptoms and other neurotic manifestations, which must be regarded as an expression of more complicated, intrapsychical mechanisms. It seems then that neither "body-preoccupation" is enough to explain the remarkable difference which we have been able to demonstrate here.

During his interviews with refugee patients, the author was often struck by the difficulty the patients had in talking about their psychic symptoms, while they had no such difficulty in recounting their somatic complaints. This was not a result of difficulties of language, but was in all probability, a consequence of the feeling of insecurity which dominated the patient. They did not feel as insecure as in "extreme situations", but neither did they feel so sure of their new surroundings as to be able to recount without more ado symptoms which in their own conception seemed somewhat strange and difficult to understand. It is surely reasonable to assume that, for example, a schizophrenic patient at the onset of the process will be at a loss to understand the peculiar and unnatural psychic sensations he is experiencing. Only when the personality's integrity is broken down and resistance disappears, does he accept psychotic symptoms as realities and recount them to his surroundings as such.

The same mechanism may be assumed to be present in refugee patients. Their feeling of insecurity regarding their surroundings will result in their omitting to recount their psychic symptoms and they concentrate rather on the somatic ones. What they themselves find difficult to understand, will surely

not be accepted by "the others". The most natural for them is then to concentrate mainly on somatic sensations. These are understandable, acceptable and "safe" to talk about, therefore they can be communicated without the patients, according to their own unconscious conception, "risking" too much.

CASE HISTORIES

Here follows an attempt made by the author to exemplify the above with the help of a few case histories.

Example 12. (Case 10): The patient was a Russian, Greek Orthodox, married man, born in 1913. There was no known hereditary tainting present. The father was a business man, who had been under arrest for some time, the mother also. The patient had been to primary school and had later worked in an office. He got married and had 2 children. He believes that his wife was "liquidated". He himself was under arrest for a short period in 1940, owing to some detrimental comments he had made about communism. He was sent to the front in 1941, was taken prisoner there three weeks later and sent as a "forced" labourer to Norway. After the war he worked at first for a farmer, later on in a saw-mill. As early as in 1946 he started to complain about weakness, debility, pains in the stomach radiating to the genitals, pains in the back and so on. The controlling physician reported him as being a "hypochondriac and neurastheniac constantly pre-occupied with complaints which have no organic foundation". The hospital examination showed the same result. His behaviour became increasingly peculiar, he was obviously hallucinated and he was admitted to hospital. He was then apathetic, autistic with persecutory delusions.

Followed up in 1956: the patient was reported to be suffering from massive hallucinations, feelings of passivity, and to be paranoid. Silly, empty, and without any emotional reaction to his psychotic symptoms.

Diagnosis: schizophrenia (paranoid form).

The number of somatic symptoms is however highest among the neurosis patients, and here we have examples of both the influence of the "primitiveness factor", of the "somatic preoccupation" as a result of bodily ill-treatment, and finally the feelings of insecurity which make the patient concentrate on somatic complaints. Below follow some case histories which serve as examples of the various psycho-genetic forms:

Example 13. (Case 63): A Czech, Roman Catholic, married man, born in 1909. The patient came from a good home, and showed no special neuropathic traits as a child. He did badly at school and failed his school-leaving examination. He was married, he had 5 children still living, 2 were dead. He owned a small "pub". His auto-characterization was as follows: he was not very particular about telling the truth, he was rather superficial without any special interests apart from "serving beer and writing bills", and adding these up so that the sum was big, and to get even more money into his pocket. He was never interested in politics. While under the influence of alcohol, he had agreed with a guest who had made some detrimental comment about the Communist regime. He was reported and summoned by the police, but got scared and fled to Germany, and from there came to Norway shortly afterwards. "They" had applied for farm hands, but he had never worked on a farm. He could not manage to work for the various farmers he was sent to, his back ached, and when several examinations and hospitalizations did not show anything pathological, he was admitted to a psychiatric department. He showed no psychotic symptoms, he appeared sly, and obviously below average with regard to intellect. Rather pre-occupied with his back-ache which was very diffuse.

Followed up in 1955: the patient was badly adjusted. He took advantage of the amnesty which was promised to political emigrants and went back to Czechoslovakia.

Diagnosis: neurosis, conversion type, in a primitive person.

The primitive reaction in this case is so clear that it hardly calls for further comment.

The next case history shows a "somatic self-absorption".

Example 14. (Case 71): The patient was a Czech-Jew, an unmarried man, born in 1917. His parents and 8 siblings were killed in concentration camps. He had no known hereditary tainting, He was at a teachers' training college when war broke out, was afterwards imprisoned

in concentration camps. After the liberation he was a leader of young people in D.P. camps. Owing to lung tuberculosis, he spent the following period mainly in different sanatoria, hospitals and the like. In these places he received a certain amount of training but never became a skilled worker in any special branch. After his arrival in Norway, he spent the first period in sanatoria then several attempts were made to place him in some regular employment, but all these attempts failed owing to continual sick-leaves. Every type of work proved to be either "too heavy" or "too strenuous" or "not enough consideration could be given to his health". "He had been through so much in the concentration camps, he had been so seriously ill, that no one could expect him to knock himself up again". All the somatic examinations proved negative. The psychiatric examination did not prove any psychic conflict beyond a "general lack of adjustment". He proved to be slightly sub-paranoiac, and he suggested that "people" were not particularly friendly in their attitude towards him, that they did not take into consideration his special difficulties, but no psychotic traits appeared.

Followed up in 1956: it appeared that the patient's adjustment had not improved particularly, there were repeated stays at re-convalescent homes without these resulting in any satisfactory solution of his problems.

Diagnosis: neurosis, conversion type, in a previously somatically ill person.

Finally we refer to a case history which illustrates the author's "theory of insecurity".

Example 15. (Case 91): The patient was a Czech, a Roman Catholic, married man, born in 1912. There were no evident neuropathic traits, no hereditary tainting, and he had received good professional and business training, and owned a large specialized business. He got married in 1942, and was sent to a German concentration camp shortly after. He fled from his native country in 1950, was divorced a year later, re-married in 1953 to a Norwegian woman. Before his illness he was hard-working, sociable and persevering. He was hospitalized because of an "unbearable headache", pains in the neck and "consequent" depression and difficulty in concentrating. The symptoms were so serious that the psychologist suggested the possibility of an organic (expansive?) process, and the patient was admitted to the neuro-surgical department, where, however, all the examinations showed a negative result. During the course of psycho-therapy a long list of serious psychic trauma and conflicts became evident. The patient had indeed been divorced by decree of court and his first wife had also re-married, as he himself had done, but in spite of this, the relationship between them was far from completely dissolved and this led to a strongly conflicting attitude in the new marriage. Gradually, most of the patient's problems were clarified, among others also his religious scruples regarding "mixed" marriages. His somatic ailments disappeared simultaneously with his release from his conflicts.

Followed up in 1956: the patient proved to be free of symptoms and well adjusted.

Diagnosis: conversion type neurosis.

When the author during the course of his interviews with the last-mentioned patient, touched on his somatic ailments and asked him why he always concentrated only on these, the patient answered rather innocently: "Do you really believe, Doctor, that anyone would be even interested in my personal worries, let alone report me ill on account of these? On the other hand, when I tell them about my headache and all my other pains, everyone can understand me." This statement speaks for itself and calls for no further comment.

An attempt has been made in the following to divide the 44 patients with predominating somatic complaints without any traceable organic cause into the three psychogenetic forms mentioned previously. This division is purely tentative and claims neither to be complete nor absolutely reliable. The author is also aware of the fact that a division of this kind which points only at *one* pathogenetic factor in each case will never be able to satisfy clinical psychiatric demands. When, nevertheless, he yielded to the temptation to undertake this division it was merely in order to obtain an impression of the importance of the various psychogenetic factors. The following table should therefore be regarded with all these reservations in mind.

The table seems to show that all the 3 pathogenetic factors appearing here have been of importance for the development of the somatic symptom in the neuroses, but not in the psychoses. The feeling of insecurity appears to be

TABLE I

Patients with Conversion Symptoms Divided According to the Predominating Pathogenetic Factor

				"Primitive Reaction"	"Somatic Preoccupation"	Feeling of Insecurity
Psychoses:						
Men	10	..	..	3	—	7
Women	5	..	..	3	1	1
Neuroses:						
Men	21	..	..	6	18	7
Women	8	..	..	3	1	4
In all	44	..	..	15	10	19

the most frequent predominating factor, followed by the "primitive reactions". The latter are also, no doubt, a consequence of the peculiar composition of the material with regard to socio-economical conditions and the standard of education.

Briefly we may say that somatic complaints without any traceable organic cause occur very often in refugee patients (among the neuroses in 83 per cent. of the cases). The reason for this may assumedly be found mainly in three spheres, namely, the primitive reactions, somatic preoccupation and as the most important factor, predominating feelings of insecurity.

VI. IDEAS OF JEALOUSY

A symptom which also merits closer investigation and consideration is the ideas of jealousy in refugee patients.

The phenomenon of jealousy has awakened the interest of psychiatrists ever since Pinel (1809) drew their attention to it, but it was chiefly Jaspers (1910) who in his work on "Eifersuchtswahn" brought up this question for a more systematic consideration.

Among the refugee patients we find pathological jealousy reactions in 10 cases, which is slightly more than 10 per cent. of the total material. It may be considered definite that this total is only a minimum number and that attention has been drawn only to those jealousy reactions which were both striking and socially disturbing in some way or other. The material is too insignificant to proffer a systematic survey, but it does supply a basis for a discussion which may be of interest.

In going through the case histories we find only 2 patients who are married to partners of their own nationality. The others have been married or engaged to partners of a different nationality. The following case histories may be regarded as characteristic:

Example 16. (Case 55): The patient was a Polish, Roman Catholic, married man, born in 1922. He was the youngest of 4 siblings, the father was an alcohol addict, and the economical situation in the home was bad. There was no known hereditary tainting in the family. The patient had been clever at school. He was arrested in 1939, was a forced labourer in Norway where he ran away. He contacted the underground resistance movement, and after the war remained in Norway as a result of the contacts he had acquired. He was married in 1946, but the marriage was a failure, and the living conditions deplorable as the couple had to share a flat with his parents-in-law. There was constant friction and the patient became gradually very paranoid, thought that everyone wanted to kill him, and that he was being persecuted. He was very uncontrolled, and had predominating ideas of jealousy (saw strange men in bed with his wife and so on), and persecutory delusions (his fellow-workers were Communist spies, his father-in-law the Anti-Christ and so on). There was a rapid clearing up during E.C.T. The family dared not have him at home.

Follow up in 1956: the patient was then divorced from this first wife and had re-married. He appeared to be well-adjusted and had complete insight into his illness.

Diagnosis: psychosis reactiva (paranoid form).

Example 17. (Case 26): The patient was a Czech, Roman Catholic, married man, born 1911. There was no known hereditary tainting in the family. He had grown up in a children's home. An older brother was shot by the Germans. The patient went to primary school and was trained as a skilled worker. He had rather varying employment. He was arrested in 1939 and was in various concentration camps until 1945. In 1948 he fled to Germany. Reports about him were not very good. He married a German woman and had two children with her. Even in the beginning of the marriage he bothered her with ideas of jealousy, and these became notably worse after 1950 and 1951. His pre-morbid auto-characteristic was "an irritable nature, but not nervous". He came to Norway in 1949, was poorly adjusted, the difficulties with his wife and with his surroundings increased steadily. She was unfaithful, "that was certain". He threatened to kill her, all her "friends", and finally all the assistants of the refugee organizations. He was aggressive in hospital, had to be transferred to an asylum for especially difficult patients from where he was discharged after about 1 year.

Followed up in 1956: there was no catamnestic understanding of his illness, he was still paranoid in his attitude to his surroundings. (He lived in an apartment house where he was the only one whose door, which had an ordinary lock, also had a huge padlock besides the Yale lock.) No social intercourse with his colleagues, but was well liked at the workshop. ("I care only for my work, I don't take to anybody.") He was still absolutely unshaken in his conviction of his wife's faithlessness, "you can't expect anything else of a German woman". He appeared to be emotionally cold.

Diagnosis: psychosis reactiva (paranoid jealousy in a projecting psychopath).

The case shows clearly how a projecting personality's constitutional traits very strongly affect the picture of the disorder. His lack of confidence, which was doubtlessly combined with latent self-reproach because of the "mixed marriage" is projected and manifested in unshakeable ideas of jealousy.

Three non-psychotic patients are best exemplified by the following case history:

Example 18. (Case 87): The patient was a Polish, Roman Catholic, married man born in 1919. He was the oldest of 4 siblings, and grew up in very modest circumstances. There was no known hereditary tainting in the family. He suffered from enuresis up to the age of 8. He went to primary school until he was 12 years old, and later worked on the small farm at home. He was arrested in 1943 and sent to Norway. After the war he worked at first on a farm, later as an industrial worker. In 1953, he married a Norwegian woman, and they had 1 child. The marriage was not particularly successful, the wife is reportedly stubborn and difficult and he is quite convinced that she is unfaithful, "even though he has no definite proof". He was pre-morbidly marked by a somewhat sad nature, general insecurity, sadness without any melancholic traits and without ups and downs. The matrimonial conditions became gradually worse, the patient complains of diffuse fatigue, colourless depression and indefinite conversion symptoms as well as ejaculatio praecox. The wife began to withdraw from him, and his ideas of jealousy were then further increased. This, she insisted, was completely groundless, he had been jealous from "the first moment". She showed no understanding of her husband's difficulties, and especially no understanding of his feelings of inferiority and insecurity, and often teased him about his shyness.

Followed up in 1956: the patient was well adjusted in his employment but continued to be marked by a rather depressive mood. The matrimonial conditions remained unchanged. He did not want a divorce because of the child.

Diagnosis: neurosis (character neurosis), a depressive picture with an inclination to jealousy.

In summary it may be said about these 10 patients that their jealousy reactions are marked by the general feeling of insecurity so often evident in refugee patients. In this connection it must be regarded as more than a mere coincidence that 8 of the 10 patients with jealousy reactions are either married or engaged to partners of a nation other than their own. In 6 of the 8 cases the partner (fiancé or fiancée) were Norwegian. Based on the knowledge we have of the refugees' feelings of insecurity and inferiority towards their hosts, this experience supports the former statement that feelings of inferiority are releasing or modulating factors also in jealousy reactions.

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CHANGES IN PORTEUS MAZE SCORES OF BRAIN-OPERATED SCHIZOPHRENICS AFTER AN EIGHT-YEAR INTERVAL*

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THE voluminous literature reporting the effects of cortical lesions has shown contradictory and diverse findings from the earliest studies to the present (Franz, 1907; Klebanoff, 1945; Klebanoff, Singer and Wilensky, 1954; Meyer, 1957). Some investigators found no losses in intellectual function regardless of the locus of the lesion; others, a temporary loss followed by recovery of original capacity. Still others have reported significant losses following brain damage in the forebrain or other portions of the central nervous system. But for investigators in all three categories, what did "brain damage" consist of? The neurologists Brain and Strauss have observed "The study of psychological problems without an adequate knowledge of the physiology and pathology of the central nervous system can be likened to the exploration of the uncharted seas without the aid of a compass; and yet there are many psychologists who undertake the rash venture" (1955, p. vi). And what of the criteria on which the conclusions were based? An additional source of ambiguity is indicated by the fact that the overwhelming majority of conclusions on "mental" changes by psychiatrists and neurologists have generally been based on clinical or subjective estimates. *Measurement*, a crucial factor in any study, is of special importance in studies of brain damage and brain function, although despite a multiplicity of tests, there are few measures designed with attention to their unique problems. Tests employed in many psychological studies of brain damage were originally oriented toward quite different problems and had been carefully developed and standardized on non-brain damaged populations.

BACKGROUND OF THE PRESENT STUDY

In an effort to control anatomical and psychometric variables, three related multi-disciplinary projects introduced research design, planned sampling, experimental controls and standard measurement to the study of effects of brain surgery. The conclusions of the Columbia-Greystone (CG) I (Mettler (ed.), 1949), the CG II (Mettler (ed.), 1952) and the New York State Brain Research (NYSBR) projects were unanimous; no "permanent" decrements in intellectual function resulted from psychosurgery. The present study is based on the results of re-examinations with the same four psychological tests of the Psychometric Study section of the NYSBR project after an eight-year interval. In an earlier

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summary of the salient changes in all four tests (Smith and Kinder, 1959), four factors were identified as determiners of the effects of brain insult on psychological test performance: length of the interval, site of surgical intervention, age at the time of operation, and the nature of the measure. Although all four instruments showed differences between initial and long-term post-operative effects, the changes in the Porteus Maze scores were unexpectedly definitive and illustrate the importance of the last factor, the nature of the measure. In addition, the systematic differences in maze performance between operated groups from the initial to the eight-year post-operative period best represent the effects of the other three factors.

PROCEDURE

Administration and scoring procedures of the Porteus Maze duplicated those reported by the original investigation in order to provide comparable data. The original Porteus standardized scoring was slightly revised and permitted a maximum of 19 instead of the 17 provided by the standard procedures. (For a detailed description of the slight revisions see p. 155 in Mettler (ed.), 1952.) Differences between pre-operative and eight-year post-operative scores were tested for significance by analysis of covariance. This statistical technique (Walker and Lev, 1953) not only provides for initial pre-operative differences between groups but by comparing the changes between operated and non-operated patients over the eight-year interval, takes into account long-term effects that might be due to factors other than the operations (e.g. chronic schizophrenia, ageing, prolonged hospitalization, etc.).

SUBJECTS

The population (hospitalized chronic schizophrenics) consisted of 50 patients (27 operated and 23 control) still available at Rockland State Hospital who had been part of the original 68 (44 operated and 24 control) examined in the original project. Deaths, a small number (7) of discharges, transfers, and occasional inaccessibility of the patients account for the remaining difference in the number of the present study compared to the original investigation. All subjects were schizophrenics with a poor prognosis and had been carefully screened on the basis of criteria established by several co-operating disciplines. Controls had been drawn from the same pool of patients satisfying the selection criteria.

Subjects were separated into a Younger group—mean age as of 1 March, 1957, 42 years, range 36–48; and an Older group—mean age as of 1 March, 1957, 59 years, range 54–66. (For a more detailed description of the population, see Lewis *et al.* (eds.), 1956).

THE EXPERIMENTAL FACTOR (TOPECTOMY): AREAS EXCISED

Based on the results of two earlier related psychosurgical projects, Columbia-Greystone I (CG I) (Mettler (ed.), 1949) and Columbia-Greystone II (CG II) (Mettler (ed.), 1952), only a single operative procedure, topectomy, was employed in the New York State Brain Research (NYSBR) Project. Two types of cortical ablation were carried out. In an orbital topectomy, Brodmann areas 11 (sometimes including portions of 47), 10, and Walker's area 13 were bilaterally excised. In a superior topectomy, Brodmann areas 9 (sometimes including portions of 10), 8, and 32 were bilaterally excised. More simply stated, a block of cortical tissue about the size of a half crown (or half dollar) and the thickness of 2 cm. was removed from either the lower (orbital) or upper (superior) portions

of the forebrain. Based on the practices of Pool (Ch. 2, Lewis *et al.*, 1956) the amount of cortical tissue to be removed was standardized at 30 to 35 grams from each hemisphere. For the reader not familiar with the uncontrolled aspects of brain operations, Mettler (1949) has detailed numerous complicating factors which should be taken into account in assessing the neuro-anatomical variables. However, in contrast to the "blind" lobotomy procedures, topectomy employed an "open" surgical technique which exposed the cortex and permitted more careful definition and identification of the areas and amounts excised.

ORIGINAL AND RELATED FINDINGS

Many investigators had found that generally accepted tests such as the Wechsler-Bellevue, Stanford-Binet and Rorschach revealed no marked post-operative changes. In contrast to the negative findings with these instruments, shortly following operations, scores on the Porteus Maze test revealed markedly poorer performance in numerous investigations (Klebanoff, Singer and Wilensky, 1954). In a review of recent maze studies, Porteus (1959) called attention to early deficits in the Porteus Maze scores after operation in the CG I, CG II and NYSBR projects. However, because of apparent increments in tests administered after longer post-operative intervals, the reports unanimously concluded that early post-operative losses in maze performance were temporary. In the CG I project, scores had steadily increased in four post-operative administrations until the score of the operated group on the last test (administered one year after surgery) exceeded the pre-operative level by approximately the same amount shown by the controls. In the CG II project, scores increased in two tests administered 10 and 90 days post-operatively. In the NYSBR project, decrements in single post-operative tests of different groups became smaller as the interval was increased from 10 to 30 to 90 days following surgery. Thus, while initial post-operative losses were found in each of the three studies, the reports unanimously concluded that early decrements were temporary and followed by subsequent recovery. Studies of lobotomy cases by Porteus (1944), Porteus and Kepner (1944), Porteus and Peters (1947) and others had also found a similar "drop and rise" pattern. Hence, it was not unreasonable for Landis to conclude at the third Psychosurgery Conference (1951) that all losses in the three related projects were temporary. However, Petrie (1949), Greenblatt, Arnot, Poppen and Chapman (1947), Porteus and Peters (1947) and Crown (1951) reported decrements with other populations after intervals of up to one year following operations. These contradictory results of investigations of *apparently* similar populations with the same psychological test reflect the paradoxical findings reported in the current literature in psychology, neurology, psychiatry and other disciplines studying the effects of "brain damage". Re-examinations of the patients of the NYSBR project after an 8-year interval afforded unique opportunities to compare short and long-term effects of surgery on a population of "brain-damaged" subjects that had been carefully differentiated on the basis of site and age.

RESULTS

Table I presents the means of the two pre-operative and single initial post-operative tests (administered either 10, 30 or 90 days following surgery) under Columns I, II and III, and the results 8 years later under Column IV. The careful definition of neuro-anatomical variables in the original study, i.e. the differentiation of operated patients into subjects with orbital (lower) excisions and superior (upper) excisions in the forebrain permitted comparisons of a

TABLE I
Porteus Maze: Means and Standard Deviations
Preoperative, Initial and 8-year Postoperative Scores

			I	II	III	IV	<i>I and IV</i>	
Groups	N		Pre-operative 1	Pre-operative 2	Post-operative 1	8-year Post-operative	<i>Difference</i>	<i>(a)</i>
Superiors	.. 17		13·88	14·74	11·69	10·00	—3·88*	(16)
S.D.			3·19	3·58	3·19	3·89		
Younger	.. 12		14·67	15·54	12·59	10·58	—4·09*	(11)
S.D.			2·79	3·23	3·21	4·30		
Older		5	12·00	12·80	9·70	8·60	—3·40	(5)
S.D.			3·62	3·98	2·31	2·49		
Orbitals		10	8·65	11·55	8·28	8·45	—0·20	(3)
S.D.			3·76	4·65	3·73	3·12		
Younger	.. 7		6·93	9·71	6·57	7·57	0·64	(1)
S.D.			2·19	4·15	1·51	3·09		
Older		3	12·67	15·83	14·25	10·50	—2·17	(2)
S.D.			3·82	2·52	2·47	2·50		
Controls	.. 23		10·87	11·89	12·59	10·22	—0·65	(12)
S.D.			4·61	4·92	4·35	4·29		
Younger	.. 12		9·79	10·21	11·13	9·33	—0·46	(7)
S.D.			4·44	4·92	5·15	4·94		
Older		11	12·05	13·73	14·06	11·18	—0·87	(5)
S.D.			3·93	4·41	3·00	3·42		

(a) Number of subjects showing losses in first pre-operative and 8-year post-operative score comparisons.

* Significant at the .05 level.

population that must otherwise have been lumped together as "brain operated", or "frontal lobe cases". Further differentiation of the population on the basis of chronological age at the time of operation provided an opportunity to study interactions of the effects of the site of operation with the age factor. The availability of pre-operative and initial post-operative maze scores afforded data for comparisons with the results eight years later. Thus, the differences in the effects of interaction of three factors: length of the post-operative interval, site of operation and age at time of surgery, are reflected in comparisons of changes for each operated subgroup for short and long-term post-operative tests. Although Porteus (1959) has pointed out that it is impossible to equate non-operated (control) subjects with the experimental (operated) group "in such factors as rate of ageing processes", the controls had been carefully matched on a large array of variables including age, education, length of illness and others described elsewhere (Lewis *et al.*, 1956).

The most striking difference in the effect of the interval may be observed in comparisons of its interaction with the site factor. Shortly following surgery, both major operated groups, Superiors and Orbitals, showed marked decrements below the pre-operative levels (see columns I, II and III). In view of the expected increment as a function of practice effect (shown by the controls), the magnitude of the operated losses presumably exceeded the absolute differences between pre-operative and initial post-operative scores. The initial losses for both operated groups were approximately equal.

Eight years later, however, the mean score of the Superiors (17) decreased still further, whereas the means of the Orbitals (10) and controls (23) were approximately the same as the pre-operative level. The eight-year post-operative loss by the Superiors, 3·88 below the pre-operative level (see Difference I and IV column) when compared to a loss of 0·65 for the controls, was statistically significant at the .05 level by analysis of covariance. In a direct comparison of the two operated groups, the difference between the Superiors and Orbitals was non-significant. Further definition of the significance of the difference in mean

scores may be observed by comparisons of the number of subjects in each group whose eight-year post-operative scores declined below their pre-operative level (see Table I, Column IV under (a)). The eight-year post-operative scores of 16 of the 17 subjects (94 per cent.) with superior topectomy declined below their first pre-operative score, the score of the 17th remaining unchanged. Of the 10 subjects with orbital topectomy, only 3 showed losses (30 per cent.), 5 gained and 2 remained unchanged. Of the 23 controls, 12 declined (52 per cent.) and 11 gained.

It is clear from these data that the two operative procedures differ markedly in long-term effects, although these differences were not readily apparent shortly following operation when both operated groups showed losses. The Superiors showed a loss shortly following surgery and, eight years later, a second loss further below the pre-operative level. Scores of the Orbitals, on the other hand, though declining shortly following operation, showed complete recovery eight years later and, like those of the controls, differed only slightly from their pre-operative level. Thus, for "brain-damaged" subjects with lesions in the superior or upper regions of the forebrain, the gradient of successive losses between short and long-term scores sharply contradicts the frequently reported findings of a "temporary" loss and a "drop and rise" pattern.

Analysis of interactions of the age factor with site of operation and interval revealed that superior topectomy affected both younger and older subjects in the same way; both age categories showed the same pattern: losses in the initial and eight-year post-operative tests. The long-term effects of orbital topectomy, however, differed for younger and older subjects. Immediately following psychosurgery, both older and younger orbitals showed losses (Column III). However, eight years later (Column IV), the mean score of the younger orbitals was slightly above the first pre-operative level. In contrast, after an eight-year interval, the older orbitals, unlike the younger orbitals, and like the subjects with superior topectomy, showed a second loss. Compared to a decrement of 0.87 by the older controls (Diff. I and IV), the older orbitals showed a mean loss of 2.17 below the pre-operative level. In view of the small number of older orbitals (3), this finding can hardly be considered definitive. However, the pattern of successive decrements is supported by similar decrements in four additional measures (Vocabulary, Object Assembly, Weigl Sorting and revised Capps Homograph). For all five measures, the pre-operative eight-year post-operative losses were considerably greater than those of the older controls. Since, in addition to the marked similarity in pattern to those of the younger and older superiors, this finding is logically consistent with clinical neurological and other psychological studies cited below, it is probable that the losses of the older orbitals have not been due simply to age or chronic schizophrenia.

Thus, in a population of brain-operated subjects which could be differentiated into four subgroups, three (the younger superiors, older superiors and older orbitals) did not show a "transient" loss in Porteus Maze followed by recovery. Instead of the "drop and rise" pattern, comparison of pre-operative, initial post-operative and eight-year post-operative scores showed a gradient of increasing losses, or a "drop and drop" pattern. Only a single operated group, the younger orbitals, showed recovery of initial post-operative losses or the "drop and rise" pattern so frequently reported in studies with shorter post-operative intervals.

This finding was not confined to the Porteus Maze results. Statistically significant losses by operated groups when compared to appropriate controls were reported in a total of 8 of 14 measures (Smith and Kinder, 1959). However,

the greater sensitivity and discriminating capacity of the Porteus Maze when compared to the seven other individual measures showing statistically significant decrements is clearly shown by the losses of 16 of the 17 subjects with superior topectomy. (Landis has suggested that the 17th, whose pre-operative and eight-year post-operative scores were unchanged, might have shown a loss if the test ceiling were higher, since his scores approached the maximum on both occasions.)

DISCUSSION

The four psychological tests provided 18 different measures: 14 individual test scores consisting of the 11 Wechsler-Bellevue subtests, the Weigl Sorting, revised Capps Homograph, and Porteus Maze tests; and four aggregate measures consisting of three I.Q.s (Verbal, Performance and Full Scale) and a composite score derived from the sum of the standard scores of the 11 subtests, the Porteus Maze and revised Capps Homograph. Except for the Weigl, which revealed marked long-term loss in shifting capacity by both operated and control groups, the results consistently showed statistically significant losses which had not been present shortly after operations. Although the Porteus Maze was most subject to practice effects, the maze scores provided the best illustration of the importance of differentiating the effects of four factors in efforts to assess the effects of brain insult: length of the post-trauma interval, specific site of tissue initially destroyed, age at the time of brain injury, and the nature of the measure employed.

INTERVAL

It is obvious that the results of any examination are time limited. The maze scores in the present study consisted of the means of two pre-operative tests, one initial post-operative test and one re-examination after an eight-year post-operative interval. The first three tests were administered within the space of one year. Since, as the first three scores of the controls show, this version of the Maze is particularly susceptible to practice effects, the initial post-operative loss of all four operated groups was presumably greater than the drop below their pre-operative levels. Although noting a reduced capacity to benefit from practice for the Superiors, Sheer, the original investigator, observed that the losses of the operated groups tended to decrease as the post-operative interval increased from 10 to 30 to 90 days. Since other measures failed to show marked initial losses, interpretation of a "drop and rise" pattern with the limited available data was logical and in accord with the results of the two earlier CG studies.

However, clinical and neurological studies have increasingly demonstrated that the structural and functional sequelae of brain injury vary considerably with the passage of time. Based on extensive studies of World War I cases, von Monakow and Mourgue (1928) differentiated between "symptomes temporaires" and "symptomes residuels". Von Monakow attributed initial temporary symptoms to "diaschisis", a dynamic distance effect in which the suspension of function radiated beyond the boundaries of the lesion to distant functionally related parts of the brain even though these had not been primarily injured. Residual symptoms were those ascribed to secondary neuro-anatomical degeneration. Independent studies of large numbers of World War I cases by Head (1926) and Goldstein (1939), confirmed these findings. Head called attention to the constant changes in disorders of function and pointed out that to consider clinical manifestations at any given moment as permanent and directly associated with anatomical changes in a restricted part of the brain was a

fundamental error. Head attributed restoration of function to three factors: recovery from pathological processes of a grossly organic nature, the diminution of diaschisis, and the gradual assumption at a latter stage of compensatory powers by uninjured portions of the brain. The numerous and extensive studies of Russell (1934, 1939, 1945, 1951, 1954) in addition to providing further evidence of the effects of diaschisis, emphasized the importance of the time factor. In numerous follow-up studies of thousands of World War II casualties and other neurological patients over periods of several years, Russell noted both the gradual disappearance of initial post-trauma symptoms, and in many cases, sometimes 5 or more years later, the emergence of new symptoms.

The unique opportunities for neuro-anatomical studies of leucotomized cerebra showed that time was also a determiner of structural changes following surgical lesions restricted to the forebrain. Yakovlev (1953, 1954a, 1954b) found that the amount of neuro-anatomical degeneration in patients who survived from 2 weeks to 4½ years increased with time; the longer the survival, the greater the degeneration.

Analysis of short and long-term effects of operation on maze scores is complicated by practice effects. Porteus (1959) reported a gain of about 2 years in test age after an interval of 4½ years "as a result of practice" in a non-hospital population (criminals). Although the controls in the present study are younger and older chronic schizophrenics hospitalized for not less than 10 years, their scores after an eight-year interval are practically unchanged from the pre-operative levels. It is therefore not unreasonable to assume that practice effects in the present study have affected scores after an eight-year interval only slightly, if at all. However, practice effect within the 9-month interval of the original study is evident in the two successive gains of the controls (Columns I, II and III). If we assume that the initial post-operative scores of the operated groups are inflated by practice gains equivalent to those shown by the controls, there appears to be no difference between initial and long-term losses of the Superiors. How can we be sure, then, that the long-term losses were not actually present to the same degree shortly following surgery and during the eight-year interval? We cannot. However, analyses of the available data for evidence of differences in interaction of both site and age point to systematic changes in the gradual evolution of long-term effects for all four operated groups.

Since practice effects are obviously related to the length of the interval between tests, we may reasonably assume that the practice gains after a 10-day interval should be higher than those for a 30-day interval and least for the 90-day interval. Thus scores of operated groups retested 10 days after operation may be expected to include higher practice gains (and should therefore show less of a drop below the pre-operative levels) than scores after a 30-day interval; and the scores after a 90-day interval should show the smallest practice gains (or the greatest drop below the pre-operative levels). However, the initial post-operative losses showed exactly the opposite pattern; the losses *decreased* as the post-operative interval increased from 10 to 30 to 90 days. This suggests that for all operated groups, the initial effects of operation, whether due to diaschisis or operative shock, gradually diminish within a limited period following surgery. The recovery of the pre-operative level by the younger orbitals after an eight-year interval indicates that as the initial effects of operation wear off, there is a slow but gradual restoration of function. For younger and older superiors and older orbitals, however, the data suggest that with the gradual diminution of the effects of diaschisis or operative shock, there is a slight recovery of part of the decrement, followed by later increasing losses as secondary degeneration

spreads. In the absence of pathological anatomy for the subjects in the present study, this suggested rationale for the pattern of post-operative changes may be gratuitous. However, in several other measures less susceptible to practice effects, the patterns of post-operative changes for all four groups showed a high consistency. Statistically significant losses, which had not been present shortly after operations, were observed in several measures for the younger and older superiors and older orbitals in comparisons of pre-operative and eight-year post-operative scores (Smith and Kinder, 1959). The younger orbitals, however, did not show a single statistically significant long-term loss. Further evidence in support of the suggested rationale for the systematic changes in post-operative scores is afforded by the striking consonance with neurological findings in comparisons of the factors of specific site and age.

SPECIFIC SITE

One of the factors differentiating the unquestionably "brain-damaged" population of the present study was the surgical definition of the brain insult. By removal of approximately the same amount of tissue from each hemisphere in open standardized topectomy procedure, comparisons of the effects of two different ablations provided evidence of possible differences in effects on psychological tests as a function of the specific areas removed. Despite the gradual accumulation of consistent and definitive findings of marked differences in effects of brain injury as a function of the specific site of injury in human subjects, many investigations adhere to Lashley's concept of equipotentiality, which was based on studies with rats.

The results of the present study show clearly that destruction in the superior portion of the forebrain results in greater losses than destruction of the same amount of tissue in the orbital region. These results are in accord with findings of other psychological studies cited by Porteus (1955), Petrie (1952), Crown (1951), Penfield (1948) and Malmo (1947). Although the studies cited were based on changes within a limited post-operative interval, and data for long-term effects are lacking, they are consistent with the results of clinical and neurological studies.

Brain and Strauss (1954) found the exact plane of cortical incision in leucotomy as being of "the greatest importance. If it is too anterior, the effects of operation will be small; if it is made too far posteriorly, the effects will be profound, amounting in extreme cases to the organic-reaction type of psychosis and dementia" (p. 24). Pool, who introduced topectomy, later (1951) reported similar findings; "deleterious effects" followed more posterior ablations "probably due to the additional quantity of brain function thereby disconnected". Le Beau (1952, 1954) reported that destruction of the posterior portion of Brodmann area 9 and areas 8 and 6 resulted in loss in intelligence while ablations of more rostral areas did not.

In a review of temporal lobe studies, Milner (1954) called attention to similar differences in effects on mental performances as a function of the specific areas destroyed in the temporal lobes. (It is interesting to note that in one of the studies cited, Weisenberg and McBride (1935), the Porteus Maze, compared to other measures, "notably" differentiated the experimental group from the controls.) Two of the many excellent features of Milner's review were the careful consideration of differences in the anatomical character of brain tissue destroyed and variations in neuro-anatomical degeneration as possibly significant factors related to psychological sequelae of temporal lobe lesions.

The previously cited neuro-anatomical studies by Yakovlev (1953, 1954a, 1954b) in addition to demonstrating a positive correlation between survival time and the amount of secondary degeneration, also provide a logical rationale for the differences in long-term effects between orbital and superior topectomy in the present study. More marked and sometimes "massive" degeneration was found in the cerebra of leucotomized patients with posterior cuts compared to little degeneration for more anterior lesions.

These consonant findings not only contradict the theory of equipotentiality in the human brain; they clearly differentiate areas within the larger structures, the frontal lobes and the temporal lobes. Thus, the equation of patients with a variety of lesions under such classifications as "brain-damaged" or "frontal lobe cases", "temporal lobe wounds", etc., introduces ambiguities owing to the lack of differentiation and implied equipotentiality of areas within more or less arbitrarily defined larger structures in the brain. The neuro-anatomical studies of lobotomized subjects (Meyer, Beck and McLardy, 1947; Eie, 1954; Le Beau, 1951) have consistently shown a considerable difference between what the surgeon thought he cut and what he actually did cut. The possible variations in specific site of leucotomy lesions may therefore constitute a basis for reconciling the apparently contradictory findings of psychological studies of the effects of leucotomy.

AGE

The careful selection of two different age groups (with a 17-year difference in mean ages and no overlapping of ranges) equated for symptoms, length of hospitalization, minimal education, and site of surgical intervention afforded a unique opportunity to study the effects of interaction of the first two factors, length of post-operative interval and specific site, on a third factor, age. The evidence of previous psychological studies of this last factor is understandably meagre. Swartzlander (1952) reported that losses in 19 lobotomized subjects occurred more frequently in subjects over 30. Frank (1946) found similar losses after one year only in leucotomized patients over 55. Lashley (1938) cited numerous animal studies showing the importance of age as a factor limiting recovery of function following brain injury.

In view of the small number of older subjects in the present study, the findings can hardly be considered definitive. However, the greater losses of older operated subjects after an eight-year interval show an internal as well as external logical consistency. The "drop and drop" pattern of the older orbitals, clearly shown in the maze scores for the two post-operative tests, was also shown in other measures which were not markedly affected shortly following surgery. Externally, the results in psychological test performances are in accord with the findings of neurological studies by Meyer (1949) and Le Beau (1951). The cerebra of older operated subjects showed more marked degeneration than those of younger operated subjects. After extensive follow-up studies of large numbers of brain-injured cases previously referred to, Russell reported a positive correlation between age and post-trauma symptoms including loss of memory or mental ability and concluded that age of the patient was the most important single factor determining the sequelae of head injury. Age was also cited as one of the first factors determining the effects of diaschisis by von Monakow and Mourgue (1928). A moment's consideration will show that findings of greater loss in older brain-injured subjects are not remarkable. Cajal (1928) has described in detail the "exquisite" sensitivity and more marked vulnerability of nervous tissue when compared to other histological elements.

Since the effects of age on other human tissues are readily observed in arteriosclerosis (and the critical role of the vascular supply in the brain should not be overlooked), the more pronounced effect of lesions on older cerebra should not be surprising.

In view, therefore, of the supporting neurological and clinical evidence, the meagre data of changes in the Porteus Maze and other measures for a few subjects should not be discarded. Additional data for other comparable brain-operated subjects are required before this finding of the present study can be properly assayed.

NATURE OF THE MEASURE

The Porteus Maze was one of the four psychological tests (selected from approximately 100 considered for the CG I study) that were employed in all three related projects. Of the 14 individual and four aggregate measures afforded by these four instruments, it was the most sensitive indicator of early and long term post-operative changes. Several individual measures, I.Q.s and Wechsler Deterioration Indices failed to reveal marked post-operative changes. The systematic post-operative changes (i.e. increasing losses by three operated groups and recovery of initial post-operative decrement by the fourth) were best reflected by the successive maze scores. For the group showing the most marked losses, the 17 Superiors, 16 showed long-term decrements, the score of the 17th remaining unchanged. A possible explanation for the differential sensitivity is that Maze performance requires selective capacities that are vulnerable to brain insult. The Porteus Maze Test (1914) is one of the oldest psychological instruments in use today, but despite numerous studies, external validation has not been achieved. The precise dimensions measured by the test cannot be unequivocally defined. However, its sensitivity to initial changes following brain insult has been abundantly demonstrated in numerous other studies of brain insult where other measures were only slightly, if at all discriminating. Further analytic study of the numerous complex physiological, psychomotor and psychological elements involved in maze performance—i.e. vision, perceptual field organization, psychomotor co-ordination, attention, selection of a response in a choice situation, impulsiveness, planning, immediate memory, learning rates, etc., may contribute to the isolation and identification of the nature of the specific components that are affected by brain insult.

The definition of four factors cited above are limited to the present study and its unique population. However, the unusual consonance of systematic changes in maze scores with the findings of independent neurological and clinical studies suggest that the results may be a psychological analogue for similar structural and behavioural changes observed by investigators in other disciplines. In addition to these four factors, the systematic differences between initial and long-term effects of operation are logically consistent with the effects of diaschisis, and differences between initial and residual symptoms observed by von Monakow, Head, Goldstein and Russell cited above.

These findings suggest that the paradoxical and contradictory conclusions of many studies of *apparently* similar populations of "brain-damaged" subjects with the same psychological instruments may be reconciled if the four factors can be taken into account.

SUMMARY

1. Eight years after the New York State Brain Research project, 27 operated and 23 non-operated hospitalized chronic schizophrenics, of an original population of 44 operated and 24 non-operated subjects, were re-examined with the Porteus Maze, the Wechsler-Bellevue I, revised Capps Homograph and Weigl Sorting Test. Analysis of the results of the Porteus Maze, which best represented the salient changes with all measures, showed systematic differences between initial and long-term post-operative effects.

2. In contrast to conclusions of a "drop and rise" pattern and "no permanent deficits" in intellectual functions by the original and two related Columbia-Greystone studies, scores eight years later showed statistically significant losses for operated groups in the Porteus Maze and seven other of the 14 individual measures.

3. Changes between initial and eight-year post-operative effects were related to four factors (a) length of the post-operative interval, (b) specific site of surgical intervention, (c) age of the subject at time of operation, and (d) nature of the measure. Of the four operated groups, only younger subjects with orbital topectomy failed to show successive post-operative losses.

4. The pattern of increasing decrements in psychological test scores is consonant with findings of increasing neurological degeneration reported in studies of cerebra of other subjects with psychosurgical lesions. The rate and amount of degeneration were found to be positively correlated with the factors of length of post-operative interval, site of surgical intervention (posterior lesions result in greater degeneration than anterior lesions) and age of the subject at the time of operation. This consonance suggests that changes in test scores may be the psychological analogue for neuro-anatomical changes due to later secondary degeneration.

5. Differences in long-term effects of excisions of lower (orbital) and upper (superior) portions in the forebrain contradict the theory of equipotentiality of areas in the "frontal lobes".

6. Comparisons of early and later post-operative effects on older and younger subjects with orbital or superior topectomy clearly illustrate the complex and dynamic temporal nature of the effects of "brain-damage". The effects of diaschisis or post-operative shock and the influence of the four factors cited in (3) above indicate that the reliability and validity of findings of any study are limited to its particular post-trauma time span. Results obtained shortly following brain insult are least reliable. The diverse and contradictory conclusions of many studies of apparently similar "brain-damaged" populations may conceivably be reconciled when the above factors are taken into account.

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VISUAL THINKING AND SIMILAR PHENOMENA

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1. INTRODUCTION

THE aim of this paper is to investigate some para-hallucinatory visual phenomena, to classify them into certain groups, to describe their phenomenology, and to try to explain their psychodynamics and their significance in everyday life.

2. "VISUAL", "ARCHAIC" AND "AUTISTIC" THINKING

Various visual experiences of a para-hallucinatory nature represent the pseudo-perceptual projections into the visual space of the subject's sub-conscious wishes, fears and vague notions (cf. Lukianowicz, 45). These, in turn, are a part of our subconscious *thought-content*. Thus, different visual experiences, representing such wishful, vaguely formulated or disguised thoughts, are, in fact, a pictorial or visual expression of the thought-process. This visual way of thinking is usually complementary to the "ordinary", more common, way of thinking by means of words, i.e. to verbal thinking.

Each of these two fundamental ways of thinking possesses certain characteristic features. Thus, *Verbal Thinking* is the product of the conscious part of the mind. It is formed of ideas expressed in words, is directed by logical associations, and aims at the solution of certain problems in real life, by means of a deliberate reasoning and calculation. The other type of thinking, employing visual images for its expression, or, as we propose to call it, *Visual Thinking*, is the language of the unconscious mind. It usually has a compensatory mechanism, a wishfulfilling character, it indulges in fantasy, and often is detached from reality.

As visual thinking arises from the unconscious mind, it often appears to be entirely "independent" of the conscious mental content of the thinker, and displays a considerable "*autonomy*" (e.g. hypnagogic imagery; eidetic obsessional imagery, etc.). In some extreme cases the subject indeed possesses no control over these pictorial "thoughts", and can neither abolish them, nor change their contents. Because of this dissociation from the conscious part of his mental life, these experiences are often felt by him as "foreign" to his "normal" (i.e. conscious) thinking, and do not appear to be an integral part of his personality (an analogy with the "voices" in auditory hallucinations).

Sometimes, particularly in their more bizarre form (e.g. as occurring in psychoses, or in dreams), these visual phenomena seem to stem not from the unconscious mind of the given individual, but from the racial, or *collective unconscious* (cf. Jung, 32, 33). They are identical with those often met with in myths and folklore, and are called "*archaic*" or "*archetypal images*".

According to Jung, we all harbour, in a latent form, these archaic modes of thinking. However, they are repressed in the unconscious strata of the mind, and normally, in waking life, they only occasionally break through

the surface of consciousness, disguised as certain irrational fears, some bizarre fantasies, vague and odd notions, peculiar "visions", etc. However in sleep, when the censorial function of the ego is not at its full waking strength, they may emerge from the mysterious darkness of the unconscious in the form of "bad dreams", nightmares and "sleep-hallucinosis". Yet only when the ego becomes considerably weakened, as for instance in a spontaneous psychosis, or in an experimentally (cf. Prince, 57, 58, 59, 60), artificially induced "model psychosis" (cf. Fischer, 15, 16), or in some intoxications (e.g. hashish, mescaline and other hallucinogenic, or "psychotomimetic" drugs; cf. Osmond, 52, 53, 54; Peretz *et al.*, 56; Sai-Halász *et al.*, 61, etc.), may these archaic images dominate the whole conscious mental content in the form of fantastic "visions", bizarre hallucinations, and odd delusions, without an insight into their unreal nature.

It has been assumed that wishes and fears are the basis of visual thinking. Similarly, "Wishes and fears constitute the contents of *autistic thinking*" (Bleuler, 7), which "is directed by affective needs", is performed "in symbols, in analogies, in fragmentary concepts, in accidental connections", and "is the source of the delusions . . . and all the other pathological symptoms". Further, like visual thinking, autistic thinking, which Bleuler regards as "an exaggeration of a physiological phenomenon", is normal in children, and, as it is in the case of visual thinking, "A large part of poetry, our tales and myths, have their source in this kind of thinking" (Bleuler, 7). Finally, as in visual thinking, ". . . we find evidence of inadequate or absent distinction between fantasy and reality in dreams, in states of absent-mindedness, in children who tell lies without knowingly lying, and in the 'savage'."

Autistic thinking has also many common features with archaic imagery. Thus, like the latter, autistic thinking is met with in dreams, in hypnagogic and hypnopompic imagery, in day-dreams, and also in individuals in whom the higher mental faculties (i.e. the ego) became temporarily or permanently weakened or deranged, as e.g. in some intoxications, in artificially induced or in spontaneous psychoses, as well as in prolonged sensory deprivation (cf. Vernon *et al.*, 71).

McKellar (48) divides the thinking into the following two groups: (1) "R" (reality adjusted) *Thinking*, a process of reasoning, logical, realistic and prejudice-free; and (2) the Bleulerian "A" (autistic) *Thinking*, characterized by "the inner, fantasy life", and defined by Warren (73) as "a type of thinking dominated by subjective trends, the material being uncorrected in its essential features by objective standards, e.g. day dreams".

The resemblance between our verbal and this "R" thinking, on the one hand, and our "visual" and the "A" thinking, on the other hand, is quite obvious, and the conclusion may be drawn that they are either closely related, or identical.

Visual thinking is the philogenetically and ontogenetically older and more primitive type of thinking, produced, motivated and directed by emotions, unconscious wishes, and fears. Hence it is irrational, illogical, and unrealistic. This non-verbal, or rather *pre-verbal way of thinking in visual images*, is characteristic of the pre-literate social groups. In this respect it shows a striking similarity with the *pictorial writing*, through which all human races seem to have had to pass in their evolution to a more advanced way of writing, by means of signs and symbols. Yet, even today the pictorial writing survives as the only form of writing in some primitive social groups,

whilst the strictly symbolical *verbal writing* is the accepted form of communication in the more advanced and more civilized societies (cf. also Tylor, 69). In our own culture the pictorial way of "writing" is still used in the elementary school books, as a useful introduction to the more difficult representation of objects by means of written symbolic signs.

The pictorial way of forming and expressing their thoughts is also quite normal in *children* in the pre-school age, before they learn to express themselves in the conventional, but more difficult and more mature, way, by means of spoken or written words. However, this form of pictorial, visual, thinking loses its rationale in the period of the completed mastery of the spoken, and later of the written, language. Hence it gradually retreats and is substituted by the verbal, at first concrete, thinking, which in turn becomes increasingly abstract. The disappearance of visual thinking is enhanced by the "emphasis upon abstract thinking in higher schools" (Allport, 1). Its full survival in adult life is not only extremely rare, but rather abnormal. It then may be regarded either as the *fixation* at, or as a *regression* to, a less mature, more primitive, pre-verbal type of thinking. Hence Kroh (41) called the poets with a very strong visual imagery "grown-up children".

3. CLASSIFICATION

With regard to its structural *contents* visual imagery may be divided into two basic groups:

(a) *Formless images* are experienced either on closing the eyes in broad daylight, or as an introductory phase to more highly organized hypnagogic images, and consist of: spots of light, bright patches, shiny spots, bright spots, stripes, clouds of light, colourful spots, blots of colour, patches of colour, etc.

(b) *Formed images* may be sub-divided into the following subgroups: (1) *Human faces* and whole human figures: they may be "seen" either in broad daylight, as in after-images and eidetic images, or before falling asleep, as in hypnagogic images. Many subjects often "see" human figures in a setting of a complex scene, resembling old silent films (e.g. in eidetic images, obsessional eidetic images, in hypnagogic and hypnopompic images and in dreams). Occasionally such "visions" may be most alarming and disturbing, and so realistic that the patient would seek reassurance, that "they are not real" (e.g. our patient "C"). Sometimes such phenomena appear spontaneously, without any conscious effort on the part of the subject, on other occasions he might "conjure" them deliberately (e.g. memory images, eidetic images). In view of the very frequent seeing of human faces in para-hallucinatory experiences Leaning (42) assumes the existence of "a special face-seeing propensity in the mind". (2) *Animals*: those seen in hypnagogic images "rarely act or move or express emotion" (Leaning). Their appearance ranges from "grotesque" to "extremely ugly and awe-inspiring". They are often perceived in natural colours. Those seen in other visual experiences are sometimes described as "grotesque" or "pre-historic" (e.g. in visual imagery in sensory isolation). They are frequently seen in a diminutive form. Animals seen in day-dreams usually possess very realistic qualities as far as their shape, size and colour is concerned. (3) *Scenes*: in hypnagogic imagery they vary "from a simple scene with a single person, to a very complex with many people moving about and acting" (Leaning, 42), and their contents are usually of pleasant character; on the other hand, the scenes visualized in wakeful obsessional imagery are mostly of an unpleasant, sometimes of a threatening

or terrifying nature (cf. our patient "C"). The scenery in dreams, like in modern plays, is of a secondary importance, and is usually reduced to a sketchy background. The main dramatic effect rests with the performers. (4) *Landscapes*: They are very common in the hypnagogic imagery of adults, and are usually described in superlatives, such as "most charming", "extremely picturesque", "glorious", etc. In obsessional visual imagery scenes and landscapes may constitute the kernel of the recurrent "visions". Here they usually represent certain places endowed with some emotional significance, either of pleasant and sentimental nature (e.g. images of places connected with one's childhood), or, more often, of a terrifying character, brought about by some traumatic experiences (e.g. places where one witnessed an accident, or a disaster).

Several other criteria may be employed in the classification of the parahallucinatory visual phenomena though none of them is wholly satisfactory. Thus, one may use as a guiding principle the *degree of consciousness* retained during the experience, and accordingly group the visual phenomena into: (1) the "*waking fantasies*", which include phenomena occurring during the full wakefulness (e.g. the eidetic imagery); and (2) the "*hypnotic fantasies*", occurring either in sleep, or in the drowsy state immediately preceding sleep, preceding the return to full wakefulness after sleep (i.e. dreams, hypnagogic and hypnopompic imagery). Finally, one can classify visual phenomena on the basis of their *increasing structural complexity*. A combination of these two principles will be applied on the following pages.

4. PHENOMENOLOGY

(a) WAKING VISUAL PHENOMENA

1. *After Images*

They are a physiological phenomenon, based on certain functional peculiarities of the optic organ, and are inherent to all mankind. An after-image consists of two phases, a positive and a negative one. The *positive image* is due to a continued activity "of receptors and neural processes after the stimulus has gone. It has the same colour and brightness", as the stimulus itself (Munn, 51). It lasts only a short while, and is replaced by a *negative image*, which is complementary to the stimulus in both hue and brightness. In everyday life one is not aware of either phase. However, in some unusual or morbid conditions (e.g. in obsessional states) after images may persist unduly long; further, they may be brighter and more colourful, and may show more details, than the mere physiological after images normally do.

There are two schools of thought, with two different interpretations, of this phenomenon: (1) Drever (12) thinks that "after image" is a term "erroneously used for after-sensation". Allport also believes that: "after-images belong to *sensation*, and have nothing whatever to do with memory". (2) The Marburger School regards the after images as the lowest type of progressive series of "Gedächtnissbilder" (i.e. *memory-images*), and Busse (9) suggests that after images, eidetic images and memory images represent progressively higher stages in a "teleological continuum".

2. *Memory Images*

They have been defined by Drever as a "revival of former experience of an object in the absence of the object itself". His "*primary memory image* is the very vivid memory image revived immediately after the perceptual experience of the object".

Memory images are closely related to after images and are a direct continuation of the former on a time continuum: after image—primary memory image—memory image. The duration in time, the vividness, and easiness of recall of memory images seem to depend on the *interest* and the *emotional significance*, which the particular memory image represents to the individual. In some obsessional states memory images may become unusually persistent (e.g. the face of Mr. "F" 's foreman), may show a prolonged duration and may retain their primary vividness, colour and "microscopic clearness of detail" almost indefinitely.

A memory image may be a voluntary or an involuntary one. The latter is usually connected with an emotionally charged event, or a traumatic experience, and it often shows an obsessional persistency. In this respect memory images resemble eidetic images, where, according to Kroh (40), "it is . . . the greater *interest* which one object possesses in comparison with another which gives it preference" in the arousal of an eidetic image. Allport calls this factor the "*affective tone*", and Jaensch (29, 30, 31) the "*philotropic factor*". Similarly the varying interest on the part of the "observer" is instrumental in variations of contents in visual phenomena precipitated by a prolonged sensory deprivation (cf. Grünthal, 22, 23).

The factor of interest also plays a causative part in the origin and the contents of some hypnagogic images. Thus, according to Leaning, sometimes "some scene has been vividly impressed on the senses . . . during the day, and an absolute reproduction takes place spontaneously against the background of darkness". As examples she mentions Warcollier, who visualized a test-tube, and "a mineral substance which he had been studying in his laboratory", and the report of Dr. Hyslop about a student who watched a colourful parade of Irishmen on St. Patrick's Day on a street in New York, and after a while "saw" it all over again on the dark background of the staircase. Leaning adds that "Myers classes this as a cerebral after-image"; we would rather regard it as an example of memory image (or even as Drever's primary memory image).

In spite of some similarities, memory images and eidetic images should not be confused with each other. Urbantschitsch (70) underlines the following differences: in *memory images* "a former visual perception is merely imagined", whilst in *eidetic images* "the original object is actually 'seen' ". Further, the richness in detail and clearness in eidetic images surpasses both the memory image and the after image, and "This characteristic . . . affords perhaps the best ground for distinguishing the eidetic image from the memory image" (Allport, 1).

3. *Eidetic Images*

By eidetic imagery Drever understands "a type of vivid imagery . . . projected into the external world". Klüver (37, 38) regards as an "eidetic" an individual in whom the "subjective (visual, auditory, etc.) phenomena assume a perceptual character".

Aetiologically and phenomenologically eidetic images are closely related to the just reviewed phenomena. Jaensch divided them into two groups: (1) "*The after-image-like eidetic images*", often of an obsessional nature, frequently with an unpleasant or frightening content, which "have only a slender connection . . . with the rest of the mental life", and because of that are felt by the patient as not belonging to him, and as being "foreign" to his usual "self"; and (2) "*memory-image-like eidetic images*", ". . . flexible and

changeable as memory images, willingly and smoothly following every change in the flow of ideas" (Jaensch). In Jaensch's view, these two types of eidetic imagery are correlated with two particular constitutional types, "T" and "B", which vaguely resemble Kretschmer's (39) schizothymics and pyknics, and as such are a permanent characteristic of the given individual.

The resemblance between "memory-image-like eidetic imagery" and visual thinking is striking indeed, and the conclusion may be drawn that these eidetic images are, in fact, ideas and *thoughts expressed in visual images*, and that they are identical with our visual thinking. There is hardly any important dynamical or phenomenological difference between these two phenomena, apart from the fact that memory-image-like eidetic images often may be more strictly based on visual memory, than are the free and creative images constituting visual thinking.

These eidetic images also seem to be identical with the visual experiences of the so-called "visualizers" (cf. Dewhurst, 11), i.e. individuals endowed with an unusual ability of "seeing" their mental images projected in the external visual space, with a sensory clearness and a perceptual intensity. (E.g. it is alleged that the German poet Goethe possessed a visual imagery, of almost a hallucinatory intensity and clearness. In his young days Goethe also was subject, on one occasion, to another para-hallucinatory experience, when one night he "saw" his "double"; cf. Lhermitte, 44.)

Eidetic images are perceived in broad daylight, almost exclusively by *children*, often of a high intelligence (cf. Schmitz, 62). Only exceptionally they also may be met with in some adults (cf. Galton, 18, 19). It seems that the eidetic imagery mostly persists, in an appreciable degree, only in those "normal" adults, who permanently have to use their visual imagination for their professional activity (as, for instance, painters, sculptors, poets, choreographers, script-writers, etc.).

Although Urbantschitsch makes such a sharp distinction between the eidetic images and the visual memory images, other writers see a close relationship between these two phenomena, and Allport even believes that "there may at times be a substitution of the eidetic images for the memory images, as in the case of individuals who have the ability to visualize whole pages of written material without the slightest effort at 'learning' ". (A good example of this is to be found in our patient "H".) Allport concludes: "eidetic imagery is only one form of imagination, and exists during childhood along with the ordinary 'reproductive' and 'productive' varieties of imagination."

4. *Imaginary Companions*

"They are mental images projected into the visual space and 'seen' in the perceptual field by *children* deprived of love and affection" (cf. 45), as well as by solitary children, starving from lack of playmates (cf. Svendsen, 66).

Their psychodynamics are of a *compensatory* nature: (1) "By means of imaginary companions and his identification with them the rejected . . . child can share in a vicarious way in the love and affection which his parents . . . shed upon the imaginary companions" (45); (2) An imaginary companion may represent a substitute for a desired playmate to a solitary child, endowed with a vivid and creative visual imagery.

Here is an *example* to illustrate the last point: the little son of one of Hicks's (26) close friends, an intelligent and sensitive child, invented for himself two imaginary "play-fellows", "Binny and Nurny". Until the age of 7 he

conversed and "played" with them, and they were so real to him that once, when his mother was about to take her seat at the breakfast table, he exclaimed: "O, please, not that chair. Don't you see that Nurny is sitting on it?", thus obliging her to seek another (26).

In the next *example*, Dolores, a rejected child of $7\frac{1}{2}$, tries to share in the love, which, she thought, her mother might have had for her imaginary companions, both of the sex desired by the mother, and by the stepfather, who ". . . expressed his preference for a boy many times in Dolores' hearing" (Bender and Vogel, 5). Dolores alleged: "I have two brothers. Their names are Tom and Harrison. My mother likes those names. They are not bad like me. They are very bright boys too . . .". "Well, yes, they're make-believe."

Bender and Vogel regard the imaginary companions as "a psychological mechanism used by the child to supplement deficient environmental experiences and emotional inadequacies", and Harriman (25) as "a creative impulse, like fairy-tale dramatizations, evanescent phantasy-making, and imaginative accompaniments of solitary play". The school-education represses these tendencies in children, and "real playmates cause these phantasies to disappear".

Although imaginary companions are most often met with in *children*, their occurrence is by no means confined to childhood. Thus Harriman has found them in some young *adults*, and in a modified form, they appear in visual fantasies accompanying masturbation at any age (cf. Lukianowicz, 47). Here is an *example* of an imaginary companion in *senility*:

Case I. Mr. "A", aged 78, a retired postman, suffering from a mild senile deterioration was bedridden with an extensive contracture and atrophy of both legs. He was almost blind and deaf, and could neither read, nor hear the wireless. Thus his contact with his environment was utterly restricted. To compensate for this, he created an imaginary companion: for some time it was noticed that he "saw", and conversed with "a pal of mine", whom he called "Walt". It was evident that "Walt" was the projection of the patient's idealized ego: he was "not too old", was "smart and strong", and he "could walk as much as he liked". He was "a pal, a postman", and the patient had long and friendly chats with him. On the other hand, when "A" sometimes wetted or soiled his bed, it was not his own, but . . . "Walt's" misdoing. Then he addressed his former "pal" officially as "Walter Wycomb", or even "Mr. Wycomb". On such occasions poor "Walt" would turn into a scapegoat: "He is a bad man. He is no longer a friend of mine. He is a dirty old man. He soiled my bed." The versatility and usefulness of this imaginary companion was astonishing, and his wishfulfilling and compensatory nature was beyond any doubt.

This case resembles a female patient described by Weinstein *et al.* (74), who, after an operation for a brain tumour, claimed to possess two "twin" sons: "Willie", a personification of all the good qualities, and "Bill", who embodied all the bad traits and trends. (In fact, she had only one son, William.) She exemplified the phenomenon of a "reduplication of person" (74), analogous to the compensatory reduplication of a paralysed body part.

The *insight* in patients with imaginary companions resembles the one met in other similar phenomena, in particular in eidetic imagery, and in autoscapy: on a closer examination it may usually be demonstrated that the subjects concerned are "privately" aware of the unreality of their pseudo-perceptions and of their "make-believe" character. This notion, although at first denied, seems to be very near to the surface of consciousness.

5. Autoscopic Images

These have been described by the present author in a separate paper (cf. 45), and will be dealt with here only very briefly. Autoscapy has been defined as "a complex psychosensorial hallucinatory perception of one's own

body image projected into the external visual space" (45). Some writers (e.g. Todd and Dewhurst, 68) regard autoscopia as the expression of "a psychical atavism". Psychodynamically it is closely related to the archaic images, the archetypal visual "thinking". Autoscopical images are of a very brief duration, and in most cases last for a few seconds at a time. They may appear at different intervals, and their course is unpredictable. In some patients they occur only once in a lifetime, in others they may be a daily occurrence.

Autoscopical images possess many features common with other parahallucinatory experiences. For instance, they are always projected externally, and literally "seen" in the visual field, usually with a sensory clearness and vividness. Further, like many other similar phenomena (e.g. memory images, eidetic images), they "behave" with a considerable "autonomy", and a complete disregard for their "original's" conscious effort to make them disappear. They also "ignore" physical laws, e.g. the law of gravity (cf. Lipmann's cases quoted in 45). Here is an *example* of an autoscopical "double":

Case 2. Mr. "B", a married man of 44, an electronic engineer, with an I.Q. of 133 during his treatment here (in July, 1959) for an atypical depression, disclosed the following: "In the fight for Arnhem in 1944, I sustained a head injury, and was unconscious for 2 to 3 days. When I came round, I became aware of somebody being present in the room, on my right side, very close to me. After a while I reached out with my hand, but could not feel anything." Ever since he frequently has dimly "seen" somebody, either on his left, or his right side (mostly on the right). "It was like a shadow, or a silhouette of a man", always assuming the postures adopted by the patient, and mimicking all his movements. "At first I thought that it was my own shadow, and I just dismissed it from my mind. But after a few days I noticed that this 'shadow' would appear in the wrong place, and on the wrong side, i.e. between me and the source of light". "B" became intrigued and started 'watching it'. He soon found that, "the 'shadow' would only appear when I was alone in the room. It would turn out on my side, in such a way, that I could see it only from the corner of my eye. If I turned rapidly my head, to take him 'unaware', the 'shadow' would move simultaneously, always occupying the same place in space with regard to my own body." It seemed to appear exclusively on the fringe of "B's" field of vision, so that he could never "see" it full-face. "I then started consciously to dilate my pupils and thus to enlarge my field of vision, so that I might see him more fully. But I still could see him only from profile. Then, one evening, shortly before I left the hospital, it just happened . . . Quite suddenly I could see him, without turning my head or my eyes. It was a sort of 'inner vision'. I could view him from all sides, and see all details of his figure and his clothes, and the features of his face. And then, you can imagine my shock, when I recognized in him *my own features*. It was me, or my 'double', gazing at me, like in a mirror, with a startled eye and a puzzled face." The image disappeared, when the patient closed his eyes, but he "saw" it again, as soon as he opened his eyes. "B" became frightened: "I thought I was going 'barmy'." He was too afraid to impart his secret to anybody. "However, after 2 or 3 days, I picked up my courage, and reported it to my doctor" (or rather to his surgeon, because he was then in a neuro-surgical unit). "He looked at me steadily for a while, and then said, significantly: 'Take it easy man. You will be all right, but if you 'see' yourself again, you just tell me, and I'll send you to another hospital, a special one for this sort of complaint'. I was sure that he thought I was mad, and that he was going to send me to a mental hospital." After this discouraging encounter with his surgeon, "B" never again disclosed to anybody the existence of his visual experiences.

"As time went on, I became so used to seeing 'him', i.e. my 'double', that I became almost unaware of his existence. Only when I think of him, would I perceive him again. Sometimes, for no reason at all, I might at once become aware of him, and 'see' him." At first "B" usually "saw" his "double" only sideways, i.e. his profile, "but now I can see him from any possible position, from behind, as well as from his front, just as if I was walking around him, and choosing the position from which to look at him. He is absolutely identical with me in every detail of his features, expression of his face, his dress and movements." The "double" does everything the patient does in the given moment. "B" accepted the existence of his "other self", and developed a warm affective relationship with him. He regarded "him" as a part of himself, and felt quite happy about their queer "symbiosis": "Often I even consider him to be the better part of myself, a sort of my 'ideal spiritual self', and he often has a beneficial influence on my behaviour." In other words, this "double" acquired all the qualities of a "displaced", or extrajected, ego-ideal. (In this respect it resembles the phenomenon of "reduplication of person", described by Weinstein.) "I get along with him quite well, and often converse with him, just in my mind, not aloud. I would call this an 'internal speech'. I also can hear him in my mind, never with my ears, talking to me, and giving me some advice."

6. *Visual Images in Some Obsessional States*

Any of the just described phenomena may appear, in a varied degree, in certain obsessional states. However, most frequently met there are *eidetic images*, particularly those belonging to Jaensch's "after-image-like" group. In some cases they acquire an obsessional persistence, and recur against the patient's will (as for instance, in some day-dreams, and in some characteristic childish "fears"). Such *obsessional eidetic images* are by no means restricted to a mere reproduction of a previous perception. They often may represent some simple creative imaginary quasi-perceptions, and in some extreme cases may become almost indistinguishable from common visual hallucinations.

The obsessional pseudo-perceptual experiences may be divided into two primary types: (a) *non-verbal obsessions*, including visual experiences (e.g. "I can't get the picture of a graveyard out of my mind"), and auditory obsessions ("expressed by 'I can't get that tune out of my head'", Skottowe, 63); (b) *verbal obsessions* (most often some blasphemous or nonsensical words or phrases), likewise "... may appear in the auditory or visual perceptual field; the patient may say it is as if the words were repeated and he could *hear* them inside his head; or he may say that he seems to *see* them in letters before him" (Skottowe, 63). (This last example closely resembles the visual hallucinations of our schizophrenic patient "E", where the printed words jumped out of the mouth of his "policeman".)

It is important to differentiate such obsessional experiences from ordinary hallucinations. Skottowe points out that: "Obsessions are located by the patient in his head", and "comparable remarks apply to visual verbal obsessions". On the contrary, in true hallucinations, the perceived phenomena are almost always projected, i.e. they seem to come from outside the patient's body, and only exceptionally may be localized within his head or other organ. Yet, this is by no means an iron rule. For example, all our obsessional patients quite definitely localized their visual experiences *outside* themselves, projected into the normal external visual space. On the other hand one of our schizophrenic patients insists that he "hears" the "voice of a spaceman" (who hides in ... the patient's abdomen), *within* his head. Another schizophrenic patient frequently hallucinates "five little rosy piglets. They must be within my head, because when I close my eyes, I can still see them, and that proves that they are in my head. How is it possible, doctor, to have little pigs in one's head?" Hence it may be often extremely difficult to draw satisfactorily a dividing line between certain obsessional visual experiences and "ordinary", or common, visual hallucinations. Only by considering the whole clinical picture one may be able to find, where the obsessional syndrome ends, and the psychosis begins. However in certain, fortunately rare, cases even that may be impossible to state. This particularly applies to the patients, who "... may be seen in a transitional phase in which the content of obsessional thoughts is beginning to be projected in the form of delusions or hallucinations" (Skottowe, 63), i.e. where an obsessional neurosis turns, as it were, into a psychosis.

Visual Images in obsessional states usually have their course and duration influenced by the underlying neurosis. On the whole they show the tendency to prolonged duration, with recurrent exacerbations and remissions. Here are two examples of *obsessional visual imagery*:

Case 3. Mr. "C", a married man of 52, a commercial artist, had to deal with a liquid containing cyanide in the course of his professional activity. In the Spring, 1956, after the sudden death of his father, "I became afraid that I might contaminate the sandwiches of my friends at work with the cyanide, which could accidentally remain on my hands" (an

obsessional fear). To prevent this possibility, he started a most painstaking obsessional handwashing. However it did not alleviate his phobia. Moreover, "I became afraid that I might bring traces of cyanide on my hands to my home, and poison my wife and my son. Soon I could see myself coming home and contaminating food, and could see my wife dropping instantly dead from this horrible poison" (obsessional visual images). "C" reacted to these "fears" and "visions" with an acute neurotic depression (introjected death-wishes). This, as well as his unpleasant visual experiences, disappeared after treatment.

However, in February, 1957 he developed an obsessional "fear", that he might . . . strangle babies met in prams. "Soon, whenever I closed my eyes, I always could see myself bending over prams and squeezing the babies' necks" (obsessional visual images). "I also had these 'visions' at night, with my eyes opened or closed" (hypnagogic images). "I had them in my dreams, and also in the morning, just after I woke up, but before I opened my eyes" (dreams and hypnopompic images).

After another course of treatment these obsessional "visions" disappeared, but in June, 1958 they became replaced by his old "phobias" of contaminating his family with cyanide. Soon this "fear" completely incapacitated him, and the patient stayed at home to prevent any possibility of getting in contact with cyanide. But staying at home did not dispel his obsessional fears. Moreover, he again developed visual experiences, of almost a hallucinatory intensity, in which he "saw" himself "getting up and rushing to a dumping place near the old factory, where before the war they used to dump the waste materials from the factory. I can see myself going there, soiling my hands in the refuse, and then coming back home and dropping innocently in the chair, as if nothing had happened. After a while I would see myself slipping out to the kitchen or to the pantry, and tampering with food".

Case 4. Mr. "D", a single man of 23, a maintenance engineer, treated here in December, 1958, was an immature, "shy", embarrassed individual, complaining of seeing, almost continually, a . . . mouse: "He is life-sized, has a brown-grey colour, and shrewd little laughing eyes, and he is with me all the time. I know that he is only my 'imagination', but he looks so real that sometimes I can't help bending down and trying to catch him. Then he at once disappears." "Often I deliberately cross the busy streets, hoping that one day he might get run over by a car or bus. But before I reach the other side of the road, he is already there, as if waiting for me . . . I started seeing him over 7 years ago, just before my father died, or maybe just after his death. I'm not sure if that might have had anything to do with it."

"D" also had hypnagogic experiences, in which he saw either his mouse, or the cars, which attracted his attention during the day. All these objects always rushed at him, growing at the same time larger, and when they were just going to crush into him, he would shudder and either wake up with a start, or would fall asleep.

This monotonous, "*monosymptomatic*" visual obsession of "D" resembles a case reported by Skottowe, where "A professional man complained that he could not get the idea of a certain signature, (not his own, nor that of anyone he knew) out of his mind; he would see this signature, as it were, overprinted on any documents that were before him; it would obtrude itself into his mind when he was addressing an audience in the course of his work; he would lie awake at night thinking about it."

7. Visual Hallucinations

Drever defines a hallucination as "an experience having the character of sense perception, but without relevant or adequate sensory stimulation . . . usually thought of as restricted to abnormal or pathological mental conditions".

The *criterion of "sanity"*, used for dividing these complex visual phenomena into two distinct groups, one occurring in "normal", and the other occurring in "abnormal" subjects, is entirely an arbitrary one. It is more a legal than a strictly medical concept, and it rather confuses the issue instead of clarifying it. Moreover, many contemporary writers (e.g. Dewhurst, 11; Dawson, 10; Smythies, 64) express the opinion that "ordinary" visual hallucinations occasionally occur in mentally entirely "normal" individuals, and Blackburn (6), after stating that "Hallucinations occur more frequently when a person is very tired than when he is fresh", gives the following examples of such "hallucinations" in normal people: "A person . . . who spends a whole day typing may get a visual and kinaesthetic hallucination of typing afterwards. Or, after spending a day in a boat on the river, he may continue to feel the rocking movements. Or, after spending a day at Niagara Falls, he may continue to hear the sound of the falling water when he is in bed that night 50 miles away". (N.B. one may argue that the above after-sensations are, in fact,

extremely prolonged after images, or memory images, and not hallucinations in the strict sense of the word, as almost certainly each individual in the given examples would have been probably completely aware of the unreality of his experiences, i.e. would have shown a good "insight" into the unreal character of his sensations.)

Yet, also the more medical *criterion of "insight"* can be no longer regarded as "watertight". For instance, Smythies expressed the view that even the lack of insight is not necessarily a proof of a psychotic condition, and Bamberger (3) described cases of eidetic imagery, where there existed an actual confusion between the eidetic images and the real objects. Yet this fact did not preclude him from regarding these visual phenomena still as eidetic images and not as hallucinations. Allport, discussing the sensory vividness and intensity of eidetic images in a child, points out that: "It is sometimes only with difficulty that he is persuaded to distrust the reality of these vivid images." The same occurs in the imaginary companions of children, where the fantasied visual images, although quite deliberately created, possess a hallucinatory vividness (e.g. the little boy quoted by Hicks, 26).

Thus the lack of "insight" by itself is not a proof that a given visual experience is necessarily a hallucination, or that the subject experiencing it is mentally "abnormal". However, it is fair to say that in para-hallucinatory phenomena of "normal" subjects the insight into their unreality is almost always retained, whilst in the common hallucinations of psychotic patients there usually is no insight, and the hallucinated objects are regarded as real.

The visual hallucinations are fleeting and shortlived, and their duration usually corresponds to the time which would be required if their action, or contents, were to take place in real life.

It may be interesting to compare certain visual hallucinations of one of our schizophrenic patients with some visual experiences of our non-psychotic subjects. His hallucinations show many features similar to obsessional eidetic images in the neurotic patients. Here he is:

Case 5. Mr. "E", a single man of 38, a painter and decorator, suffered from chronic schizophrenia with auditory and visual hallucinations. Among the latter, one was of a particular interest: for eleven years "E" had "seen" a uniformed policeman, grinning at him, making faces, and often behaving in a provocative manner. (It would be difficult not to notice the resemblance between this grinning policeman and the grinning foreman of our non-psychotic patient, Mr. "F".)

Although the "policeman" often used quite unparliamentary expressions, he took the greatest care not to speak them aloud; instead the offensive words jumped out of his moving mouth in form of typewritten or printed paragraphs, like the ones seen in "comics" for children. This behaviour of the "damned copper" would so upset the patient that he "often had to shout at him, to make him stop it". (Similarly the non-psychotic patient "F" occasionally would shout at his "visualized" foreman.) It was quite easy for "E" to "outshout" his silent opponent, and then "the copper" would smile apologetically, and would "say" in his usual way (i.e. by means of the printed words rolling out of his mouth): "That will do for now. I'm sorry, old chap. Let's be friends again."

However soon he would start it all over once more: he would appear on the wall and would begin his usual "silent conversation". But now he would keep his mouth shut, and the printed words would appear under his feet, like the text in the old silent films. The language he used in these printed communications was most discourteous, to say the least. "E" reported: "At first I would try not to look at the wall, although I saw in my mind that he was there, and heard in my head his silly talking." (Similarly the non-psychotic Mr. "B" "saw" in his mind his "double" and "heard" in his mind the "double" talking to him.) "This bastard would not stop playing his dirty tricks on me, trying hard to make me look at him; but I wouldn't do it." However after a while a growing inner tension would become almost unbearable, forcing the patient to turn around, and to face the annoying vision. Then, the whole story would begin all over again: "E" would jump at his tormentor, shouting and threatening, and thus would "frighten" him away. Yet, in spite of all this "persecution",

"E" maintained quite cordial relations with his "copper": "We are good pals, and, in fact, quite fond of each other. It is a fact, that he is often rude to me, but I guess he just can't help it", philosophically concluded Mr. "E".

These visual hallucinations showed the following features peculiar to *eidetic images*: (1) they appeared mostly on the grey background of a wall; likewise, the eidetic images "are best seen on a dark grey background" (Jaensch, 29); (2) the patient "saw" his "copper" not only in all natural colours, but these colours always appeared to him to be "very bright and rather exaggerated": in eidetic images, according to Jaensch, "the colours are more pronounced, 'brighter', or more 'glowing', than those of the test-objects"; (3) lastly, "E"'s visual hallucinations showed a remarkable stereotypy, and almost an obsessional monotony, closely resembling the mono-symptomatic "after-image-like" eidetic images of our neurotic patients "D" and "F".

On the other hand, "E"'s hallucinations show a resemblance to some *hypnagogic images*. E.g. he "saw" the printed words coming out of the mouth of his "policeman"; our neurotic patient "H" could also "see", and even read, the printed pages in his hypnagogic visions. Also one of the correspondents of Leaning (a Mr. H.F.S. cf. 43) was subject to similar experience: "I have a hypnagogic vision of a printed book which I try to read. I never succeeded in getting more than about half a line, and it is always the same sort of nonsense" (cf. 43).

There also exists some likeness of these peculiar pseudo-synaesthetic visual hallucinations of "E" to the hypnopompic images experienced by another of Leaning's correspondents, Mrs. A.W., who "often saw on waking suddenly the strange symbolic figures, with explanations of their meaning on scrolls or shields" (cf. 42, p. 356).

8. *Thinking in Visual Images*

This has already been described and discussed in the preceding paragraph, and here only a few additional remarks will be made. It has been assumed that there are two basic types of thinking, the one done mostly in visual images, and met in "visualizers", and the other, predominantly performed in a verbal form, peculiar to "verbalizers".

Pear (55) calls an individual with visual thinking a "*visile*", employing "this and the homologous terms *audile* and *motile* to designate people whose predominant concrete imagery used in reality thinking is supplied by sight, sound and kinaesthesia respectively. The person whose thinking is chiefly done with words will be called a *verbalizer*".

Thinking in visual images normally takes place in children, where: "The young child delights in conjuring up his images", and where frequently he deliberately creates vivid visual images, "for example, to accompany a story which is being told" (Allport, 1).

Although this type of thinking usually retreats after adolescence and tends to be replaced by the more mature verbal thinking, some rudiments of visual thinking, in the form of vivid "visualizations", are met among people who have to "visualize" their thoughts and ideas, before they can be produced or performed (e.g. the painters, sculptors, poets, script-writers, choreographers, film- and show-producers, etc.). However normally in none of these professions is visual thinking the exclusive type of thinking. It is rather a useful supplement to their "normal" verbal thinking. Here is an *example* of such visual thinking in an adult:

Case 6. Mr. "F", aged 49, divorced, a mechanic and fitter, was a definite "visualizer", whose thinking was normally done in terms of vivid and colourful visual images. He was so used to this peculiar quality of his thinking that in normal circumstances he was entirely unaware of it. He reported it thus: "I always see in pictures, whatever comes into my mind: when I think of an animal, I really see this animal, right in front of me; when I think of a man, I indeed perceive him with my very eyes. I know it sounds silly, but there you are. I just can't help it."

In contrast to ordinary visual hallucinations, the visual thinking of Mr. "F" was performed by means of freely-changing, wilfully directed and deliberately created visual images, which took place undisturbedly in the presence of other people. For instance, during an interview in my office, whilst looking at the stone-grey wall behind my desk, the patient could describe, very vividly, the scene of arrival of Queen Elizabeth, the Queen Mother, in Melbourne (it was at the time of her actual visit to Australia and New Zealand in winter 1958). He "saw" the Queen alighting from a launch and stepping ashore; he did "see" huge crowds on the quay, and a little girl, stepping forward, curtsying and presenting the Queen with a bunch of beautiful colourful flowers. "F" described this scene in an unperturbed, calm and matter-of-fact, manner. In a similar way he reported many other scenes which he incessantly "saw", i.e. of which he thought in his usual pictorial way.

There hardly can be any doubt at all that these visual experiences were, in fact, his *thoughts*, taking place in the form of visual images, projected into the external perceptual space, and then literally "seen" by him, with a sensory vividness and a perceptual intensity. Yet, a strict line of demarcation between this visual thinking and eidetic imagery, on the one hand, and visual hallucinations, on the other hand, may often seem to be only an arbitrary one.

As has already been mentioned, in everyday life "F" was unaware of his peculiar thinking. Only, when some of his visual images would gain an exaggerated "autonomy", and manifest an unduly prolonged duration, or an obsessional persistence, would he become conscious of their annoying existence, as occurred in February, 1958, when "F" for many weeks almost continually "saw" a life-sized image of his foreman, holding a cup of tea in his hand, and cheerfully grinning at him. (*obsessional eidetic images* of Jaensch's "after-image-like eidetic images" type.) At night, when the patient lay sleepless in bed, with his eyes wide opened, this image would again stand in front of him, so vivid and so real, "that I would sometimes forget that 'he' was only my imagination, and would shout at him: 'Get out of here, and leave me in peace. You have no right to come here' " (*hypnagogic imagery*). "F" has always been subject to a vivid hypnagogic imagery, and as a child he often had vivid "flying" dreams, which recurred at intervals, up into his adolescence.

This man was also given to other visual experiences, with an emotionally completely indifferent, or accidental, content: "Whatever I happen to see, however trivial, or nonsensical, will continue to persist in front of my eyes for hours, and I can't get rid of it". These unduly prolonged *after images* and *primary memory images* were most vivid in his childhood, causing him difficulties with learning, because he saw, *instead* of the printed lines, very clear and vivid images of people and scenes he had just seen and met in real life. (In this respect he resembles the boy reported by Jaensch, who could learn only in the early morning, otherwise he would see various scenes he saw during the day in the form of very small pictures *between* the printed lines.) When "F" grew up, these phenomena became much less pronounced and less obtrusive, although from time to time, without any apparent reason, they would become most

persistent and annoying again. They were spontaneous and independent of his will, and the more he tried to change their contents or altogether to get rid of them, the more obstinately they would stay in front of his eyes.

(b) HYPNOTIC AND PARA-HYPNOTIC VISUAL PHENOMENA

Various visual experiences belonging to this group occur in conditions connected with sleep. They are induced by restricted sensory perception, leading to drowsiness, and to an increasing breakaway from reality. Here are some of them, ordered according to their progressive complexity:

1. *Visual Phenomena on Brief Closing of the Eyes*

After the two phases of an after image die away, the visual field becomes filled with primitive, formless, unstable images, such as spots of light, blots, patches, flashes, threads, clouds of light, etc. Later there may appear some more highly organized formations, mostly various simple but symmetrical patterns, often a hexagonal or octagonal network, formed by bright or dark lines, coming together and then separating, and thus creating all the time some new angular or circular formations.

These "entoptic" images seem to be universal, and, like the after images, entirely physiological. Aetiologically they are related to both the after images, and the rudimentary eidetic images. They probably are inherent to the ceaseless activity of the optic nerve and the visual centres, possibly on the principle of a reverberating feed-back system. They appear very soon after closing of the eyes, and are not accompanied by the drowsiness so characteristic for different varieties of hypnotic imagery (e.g. for hypnagogic images).

The hexagonal "honeycomb" design seems to be particularly common, and it was reported (e.g. by Purkinje; by König, cf. 38) as mostly occurring in the hypnopompic imagery. Klüver (38) assumes that certain geometrical forms and designs constitute "*form constants*", which are found in different visual phenomena, e.g. "in mescaline hallucinations, in hypnagogic hallucinations, in entoptic phenomena, in the visual phenomena of insulin hypoglycaemia", and "occasionally . . . in fever deliriums" (38).

In some cases the visual field may become filled with more highly organized images, e.g. with architectural designs, or even with animal or human forms. On the whole, however, these more complex images are rather characteristic of a more prolonged sensory isolation. Here is an *example* of the latter:

Case 7. Mr. "G", 57, married, a retired high-ranking Army Officer, for the last two months preceding his admission in December, 1958, complained of the following visual experiences: "Whenever I close my eyes, I can 'see' the faces of my friends, right in front of me, about 3 or 4 feet away. They show a photographic likeness, and natural colours, but they appear in a sort of a circle, or an elliptical frame. Their facial expression changes, depending on the conversation. When they talk, their lips move. I can hear them, somewhere within my head, and I answer them, though in my thoughts only. Yet, they say that they can hear me quite well. Sometimes they hold nonsensical conversations, such as: 'Now, I will lift my right arm', or 'I will scratch my left ear', etc. At the same time they go through the announced movements or actions." Sometimes Mr. "G" could "see" these "visions" also with his eyes opened, in full daylight, but only when he was looking at a dark or grey background (eidetic images). He retained a full "insight", and regarded these experiences as his visual "imaginings". Although rather rudimentary, these visualizations, up to a certain degree, resemble the imaginary companions met occasionally also in adults.

The primitive shapeless images, as well as the more highly formed, perceived on closing the eyes are, as a rule, *involuntary*. An example of such obtrusive involuntary visual images was also Maury, who "could not close his

eyes even for an inappreciable second during reading aloud without having a vision" (Leaning, 42). However, in some cases such images may also be produced *voluntarily*, as was the case with Mr. "G".

2. *Visual Images in Prolonged Sensory Deprivation*

Grünthal (22) has described very interesting visual phenomena brought about by a prolonged closing of both eyes, i.e. by a partial temporary perceptual deprivation. They assumed three different forms: (1) *Photographic-like images* of faces, scenes, printed pages, etc., all familiar and well known to the observer; (2) *artistically styled images*, mostly of architectural nature, and (3) *images of animals*, formed of the initial "clouds of light". These visions, which occupied the whole visual field, manifested a complete "autonomy", and could not be produced by a hopeful expectation, or by a voluntary effort. In Grünthal's view, their content was on each occasion predetermined by the actual interest of the observer at the time of their occurrence.

Similar visual phenomena were reported by fourteen students, voluntarily subjected to an experimental perceptual isolation, involving a complete temporary multisensorial deprivation (in Grünthal's case only the eyes were closed, on the first occasion for 8 days, on the second for 3 days). These experiments were conducted by Goldberger and Holt (21), who found that the visual images experienced by their subjects "were unusual in their sudden, spontaneous appearance, their vividness, and in some instances, their 'meaningless' content". Of the 14 subjects of this experiment only 7 experienced visual images; of them 2 saw complex scenes; 2 "inanimate objects"; 1 saw architectural objects; 1 flowers; and 1 a "prehistoric animal".

In this connection it is interesting to notice that similar visual experiences, occurring after an intramuscular injection of D.M.T. (cf. Sai-Halász, Brunecker and Szára, 61), become more intensive and "assume a scene-like character", when the subject of the experiment closes his eyes.

Goldberger and Holt regarded most of these images as hypnagogic in character, and postulated that "perceptual isolation primarily tends to increase the vividness (intensity) and structure of imagery", but when unduly prolonged, it tends to weaken the ego and its ability of reality-testing, thus paving the way for possible hallucinations. In other words the censorial function of a threatened or weakened ego becomes less effective, and thus allows the archaic images to emerge from the dark underground caves of the racial unconscious. A dramatic *example* of it may be found in the romantic poem of Goethe ("Der Erlkönig") about a little boy, riding with his father late at night through a wood, and populating it with archetypal images of the "King of the Woods and his Fairy Daughters". These, apparently mythological, images were precipitated from the child's racial unconscious by his actual fear of darkness, and a threat to his ego by a temporary partial sensory deprivation (darkness).

Case 8. Mr. "H", 47, married, an aero-engine fitter, who "always was on the worrying side", attended, prior to his admission, a comprehensive course on jet-engines (hitherto he worked with piston-engines only). Almost immediately after this course ended, he joined another, more advanced, course for prospective foremen at B.A.C. (Bristol Aeroplane Corporation, the makers of the "Britannias"). During both these courses, "H" had to read some technical books, and, "As I always was more clever with my hands, than with my head I soon began to worry that I will fail in my exams" (*obsessional fears*). "Towards the end of the second course, just before the beginning of the written examinations, I could not close my eyes without seeing whole pages of my books. They were so clear and vivid that *I always could read a few lines*, before the rest of them would get misty and blurred, and finally disappear" (*persistent memory images* with closed eyes). "My nerves were all the time getting worse, and I soon began to see the typed pages of my textbooks also with my eyes

opened, particularly when I was looking at any dark background" (*eidetic images*). "I would see the same, when I was lying in bed, just before I would go off" (*hypnagogic images*). "It always was an extremely frustrating experience, because I could read only a few lines at a time before the whole picture would become blurred and would disappear".

This case is another example illustrating the growth and "spreading" of the emotionally-charged idea (the "fear" that the patient might fail in his examinations), assuming visual forms, and being expressed in various para-hallucinatory phenomena. All these experiences quickly disappeared after a short treatment in October, 1958 (and the patient passed his examinations).

Most of the visual phenomena experienced on prolonged sensory isolation are related to eidetic imagery and to a certain type of memory images, which may either re-appear with a photographic accuracy of after images (e.g. the typed pages of a book in the case of Mr. "H"; some architectural images, well known to the observer in Grünthal's description), or may be freely "re-styled" and unconsciously re-built by the creative fantasy of the "viewer". In the latter case they rightly may be regarded as one of the varieties of visual thinking, a para-hypnotic correspondent to the wakeful day-dreams. The duration of these experiences is conditioned by the duration of the precipitating sensory deprivation (apart from certain obsessional cases, as happened with Mr. "H").

3. *Hypnagogic Images*

They have been defined as: "Imagery of any sense mode, of a strongly autonomous kind and sometimes of almost hallucinatory vividness occurring in the drowsy state prior to sleep" (Warren, 73). They "are experienced more often with closed than with opened eyes", and "are more often coloured than not" (Ardis and McKellar, 2). They usually consist of kaleidoscopic quickly moving, changing, vivid and colourful, images. According to Leaning ". . . no picture can be 'held' indefinitely, and as a rule no picture ever appears twice". This last statement seems to have no application to the hypnagogic images with an underlying obsessional character, as, e.g. our case "D", and Mrs. Leaning's own correspondent, Mr. H.F.S. prove.

Hypnagogic images may be either an isolated experience, occurring once in a lifetime, or they may be a kind of a repetitive "overture", or an introduction to each act of falling asleep on each night of the year. These images usually last only a few seconds, although sometimes their duration may be considerably prolonged. Their *content* is extremely varied, and, apart from human faces and whole persons, often consists of scenes, which are "highly coloured, brilliantly lighted, very distinct, miniature in size, and contain numerous details" (Leaning, 42).

Although, on the whole, they possess a considerable "autonomy", sometimes a subject may train himself to produce hypnagogic visions *deliberately*. For instance, one of Leaning's correspondents (Mr. E.S.T.) claimed: "At times just before sleep I could conjure up the visual perception of anything I liked; e.g. faces of friends with most amusing distinctness and naturalness of detail" (cf. 43). There is a good reason to assume that our patient "G" also "trained himself" to "conjure up" some hypnagogic images, in which he has often "seen" whole "female figures, either naked, or just taking their clothes off, and inviting me to have sexual intercourse with them". They were always the images of women he knew intimately in the past. (N.B. for the last four years "G" lived in a "bed-sitter", away from his family, and only once, in all this

time, had a normal coitus. Thus, the wishfulfilling nature of his hypnagogic imagery is quite obvious.)

There are various views on the *aetiology* of hypnagogic imagery. Leaning herself regards them as a variety of memory images ("subconsciously memorized"). A confirmation of this is to be found in this statement of another of her correspondents (Miss M.C.): ". . . after cycling I see the hedgerows slipping past on either side, while I seem to be darting like a swallow down and up without effort". (N.B. the memory-image-like "hallucinations" of auditory and kinaesthetic nature, described by Blackburn, seem to fit this category of hypnagogic imagery admirably.) Ellis (14) offers this, *physiological*, explanation of hypnagogic imagery: "The eye supplies entoptic glimmerings, and the brain, acting on the suggestions thus received, supplies mental pictures to those glimmerings".

4. *Hypnopompic Images*

These phenomena occur in the drowsy state between the end of sleep and waking up, just before the subject returns to full wakefulness. Like the hypnagogic images, they show a considerable "autonomy", and independence of the subject's conscious "will". Although it is assumed that many children are able to produce deliberately and to control their hypnopompic visions, the ability to do so usually recedes in adolescence, and only very few adults can still conjure up and dismiss their hypnopompic images at will.

McKellar and Simpson (49) define them as "a perseveration of dream imagery into the waking-up process". Most often the hypnopompic images are "seen" with the eyes still closed, but not infrequently with the eyes already opened, particularly when the subject wakes up at night and opens his eyes. In most cases hypnopompic images are of *visual* character, although other sense modalities may also be involved. For instance, a girl reported by Ellis experienced *tactile* hypnopompic sensations. Also one of our own patients (cf. 46) was on three occasions subject to hypnopompic haptic pseudo-perceptions. Sometimes these experiences have an "anticipatory" character (e.g. of a ringing alarm-clock, before it really starts to ring).

Hypnopompic imagery is a much more common phenomenon than is generally assumed. For example, among the 182 students of the Aberdeen University, investigated by McKellar (48), over 20 per cent. experienced, at one time or another, hypnopompic images. Hypnopompic images are fleeting and of very brief duration. They are "autonomous", and any attempt at interfering with their contents or their duration in adults, usually results in the individual's complete waking up, and the instantaneous disappearance of the image. Here is a brief *example* of hypnopompic visual imagery: When the wife of one of our patients opened her eyes, one early morning, she "saw" her husband sitting on the edge of the bed, with his head in his hands; however after a few seconds, when more widely awake, she satisfied herself that "he was sound asleep by my side" (cf. 46).

5. *Dreams*

In this paper dreams will be discussed only in connection with their belonging to our second (hypnotic) group of visual para-hallucinatory phenomena.

Dreams show many features in common with other forms of visual imagery. Here are some of them: (a) The *contents* of dreams are produced and conditioned by subconscious desires or fears of the dreamer; (N.B. in some

primitive cultures, as e.g. among Temiar, the Malayan aborigines, the children are taught by their parents and other adults, how to dream, what to dream and how to react to their dream images; cf. Holman, 27; Stewart, 65). (b) The *thinking* employed in dreams represents a typical "A"-thinking, i.e. wish-directed and depending not upon logical connections of thought, but upon "free", emotionally directed, or accidental association of ideas and images. Hence dreams are usually illogical, irrational and perplexing. Some dreams quite evidently contain elements of archaic images (e.g. the typical dreams of Temiar, 27, 65), and as far as their detachment from reality, their phantastic bizarriere, and the lack of insight, is concerned, dreams resemble short-lasting, reversible, psychoses. Brain (8) expresses it even more drastically: "We are all temporarily insane during sleep, and our waking moments are but lucid intervals". (c) As in other para-hallucinatory phenomena, the action taking place in dreams, and the persons perceived in them, are always located *in the external visual space*. "We imagine, remember, and dream mainly in terms of our exteroceptive, spatializing senses; and our dreams are projected into an external world" (Brain, 8). (d) There is an, apparently complete, "*autonomy*" of the subjects seen in dreams, particularly in dreams of "persecutory" nature. Although created by the dreamer, they behave entirely independently of his efforts to direct their actions and words. Brain explains this extreme *externalization* by "a splitting of consciousness in which the individual becomes divided into multiple personalities, but just as in waking life there is only one 'me' and all other persons and things are external, so in dreams only one personality is linked with the physiological basis of the self. The rest are externalized".

It was often assumed that the *duration* of dreams is a considerable one, and that sometimes they may last even for hours. However the recent, controlled experiments, conducted under strict supervision, in laboratory conditions, with the help of EEG, etc., proved that an average dream lasts mostly only a few minutes, and very often much less than that (cf. Barratt, 4; Drever, 13; Goldberger, 20; Kleitman and Aserinsky, 34; Kleitman and Dement, 35; Kleitman and Engelman, 36; Walter and Yeager, 72; Wolpert and Trosman, 75, etc.). There are usually two peak periods with maximum of dreaming during each night's sleep.

Dreams are usually *colourless*, i.e. they are experienced in black and white, respectively in different shades of grey, although dreaming *in colour* is not very infrequent. Thus, de Martino (50) reported 17 per cent. of colour-dreamers among his southern college students, and Husband (28) 40 per cent. Both these writers met colour-dreaming three times more frequently among females than among males. Tapia, Werboff and Winokur (67) found "more neurotics to report dreams in colour". This fact was thought to be "mainly due to the female neurotic" in their group.

Here is an *example of a dream of memory image type*. It is based on some real facts and actual events, but at the same time it shows also a *distortion* and *condensation*, so characteristic for all dreams:

Case 9. Mr. "I", a chronic schizophrenic, a single man of 27, spent most of the last 9 years either in Barrow or in Fishponds (both together constitute "Bristol Mental Hospitals"). Whilst in Barrow, he was on two occasions under my care, but during the last 5 years he had been permanently an in-patient at Fishponds Hospital. Recently I received this letter from him:

"Sir, I attended a divine service at the picture hall last night in which a powerful arc light was shining on the left side of the hall. I was wondering if looking up at this light caused me to dream the following dream about yourself. I dreamt I had an interview with you at the Bristol Royal Infirmary. I dreamt you took me into a small room and connected a system of scientific apparatus over my head and ears and placed an oblong piece of rubber between

my teeth. Then I had an X-ray photograph taken of my brain. And I felt like a lot of powerful electrical waves passing through my brain." (Here follows one of the illustrating drawings: the patient's head with an electrode on it, connected by two wires with a transformer, and numerous curly "electrical waves" radiating from the top of his head.) "Then the dream completely faded away and I came back awoken to reality."

This dream represents a *condensed re-living* of three emotionally charged real events: (1) having had an interview; (2) undergoing an EEG recording; and (3) being given an E.C.T. Neither of the last two procedures is performed personally by me, and the patient must have been aware of it. Nevertheless in his dream he identified in me not only the physician examining him, but also the other two doctors, administering EEG and E.C.T. to him. Thus, in a typical way, he "condensed" in me three different persons, as he "condensed" in one scene three different events: one of being examined, one of having EEG, and one of having E.C.T. Such condensation is a negative phenomenon, opposite to a "reduplication" of person and of body parts, mentioned in preceding paragraphs.

Among the features particularly characteristic for dreams is the frequent appearance of *symbols*. This fact has been known for ages, and has resulted in attempts at explaining the dream by deciphering its symbols, i.e. its concealed meaning. Many *examples* of symbolic dreams and their interpretation are contained in the Old Testament (e.g. the dream of Pharaoh about the 7 fat and 7 lean calves). In classical *Greece and Rome* great importance was attached to the interpretation of dreams, and it was believed that it was possible to forecast the future from dreams. (Even today in some primitive cultures the dream still possesses a unique social importance, and, e.g. among the *Temiar* no important decision will be taken by the group "without one of its members having had a dream that prescribes a certain course of action", and "Most Temiar inspiration comes from their dreams" (Holman, 27). In the superstitious *Dark Middle Ages*, obsessed with religious questions, "witchcraft", dreams, particularly with an erotic content, were inevitably regarded as "temptations of the Evil One". In spite of this, the dreamer was held responsible, and was even punished for his dreams. In the over-rational *XIXth Century* dreams were viewed as the result of an uncontrolled play of the fantasy, not deserving any serious consideration or study.

Only the beginning of the *XXth Century* brought a more rational, more objective, and less prejudiced approach to the investigation of dreams. Freud (17) was the first to study them and to point out many features, common to dreams, folklore and mythology. Unfortunately, Freud's interpretation of dreams' symbols brought a lot of bitter and exaggerated criticism, overlooking and underestimating his valuable contribution to a better understanding not only of symbols involved in dreams, but also of the psychological forces behind the dreams, of their function, their meaning, etc.

There are many physiological, philosophical and psychological *theories* explaining the dreams, but only the following three need be mentioned here: (1) *Freud's* theory, interpreting dreams mostly as a wishfulfilment; (2) *Jung's* interpretation, regarding dreams as the manifestation of the archetypal thinking, and an expression of personal and of racial unconscious; and (3) the "biological" theory of dreams of Hadfield (24).

5. COMMENT

Various visual para-hallucinatory experiences show certain *common features*, as far as their localization, richness in detail, persistence, intensity,

"autonomy", conditions of arousal and disappearance, etc., is concerned. However only one or two of these characteristics can be here further elucidated. Many visual phenomena are perceived in intense *colours*, described by the subjects as "gorgeous, most vivid, exquisite, fantastic", etc. They seem to be *brilliantly lit*, in particular the hypnagogic, and to a lesser degree also the eidetic images. (2) Most of them are "seen" in a *distance* corresponding to the one found in real life, although they appear to retain this distance constantly with regard to the subject, irrespective of his possible movements (cf. the image of the elusive foreman of Mr. "F"). Hence the subject can never succeed in "catching" his vision (e.g. Mr. "D"). (3) Almost all of these visual experiences possess a characteristic "*autonomy*", i.e. an apparently complete independence from the subject's "will", or conscious effort. However, there are some *exceptions*. For example, our patient "G" could at any time "conjure up" the faces of his friends, and Leaning mentions that Meyer trained himself to "see" at will almost any image he wished in "natural colours and illumination". Allport reported that some of his "eidetics" were able "by an effort of attention, to cause movement within the image. Thus a carriage was made to drive away, turn a corner in the road, and so to disappear entirely from the image. People could be made to enter and leave, and to perform normal actions". It seems probable that many *children* can control their eidetic and hypnagogic images, creating and dismissing them at will. However, in most cases this faculty disappears at the time of puberty.

The *content* of para-hallucinatory visual experiences may be most varied, and seems to depend in each case on the subject's particular *interests* (cf. the visual phenomena "seen" with closed eyes described by Grünthal), his *fears* (e.g. the "visions" of our Mr. "C"), or unconscious *desires* (e.g. the frankly wishfulfilling hypnagogic imagery of Mr. "G"). In contrast to real hallucinations, and because of its compensatory or wishfulfilling nature, the content of para-hallucinatory experiences is only rarely disagreeable, hostile or frightening. In the main it is either indifferent, or pleasant, in particular in day-dreams, where the compensatory and wishfulfilling mechanism is often very obvious.

The *emotional reaction* to various visual experiences varies according to their nature and contents: (1) Some patients quite frankly "enjoy" their "visions", particularly those of hypnagogic and hypnopompic nature, and sometimes "train" themselves (e.g. Meyer; our patient "G") to "conjure up" various desired images (cf. also the imaginary companions of children and socially isolated adults). (2) Other subjects retain an unperturbed, or a detached attitude of an interested but passive spectator. (3) Only a few become apprehensive or emotionally disturbed by the contents of their, usually threatening, visual "imaginings" (e.g. Mr. "C"). All this presents a striking contrast to the frequently hostile or offensive behaviour of the hallucinated objects in psychotics, resulting in an aggressive behaviour, and sometimes violent reactions, on the part of the hallucinating patients. (It is instructive to compare the provocative behaviour of the "copper" of Mr. "E" with the smiling and benign appearance of the foreman of Mr. "F").

There obviously are no rules as far as the *frequency* of "seeing visions" is concerned. In hypnagogic images it "varies . . . from a single occurrence in a lifetime up to the habitual seeing by day, whenever the eyes are closed, and by night with the eyes open or shut" (Leaning, 42). The same, by and large, is applicable to almost all other visual experiences. For example, Mr. "G" could "see" the faces of his friends whenever he closed his eyes; Mr. "D"

"saw" his "mouse" almost continually for seven years; Mr. "F" "saw" his foreman only periodically.

In contrast to "ordinary" visual hallucinations of psychotic patients, in all visual para-hallucinatory experiences the subjects retain, as a rule, a full "*insight*" into the unreal character of their experiences. A few known exceptions (cf. Bamberger, 3) rather confirm the rule, and do not invalidate it.

There can be no uniform or specific *treatment* for such different and diverse phenomena. Speaking generally, any therapeutic effort should, in the first instance, aim at the accompanying syndrome, the underlying condition, if there is one evident. It seems that, as in schizophrenia, whatever one does to the patient exhibiting any para-hallucinatory phenomena, as long as something at all is being done to him, it has a therapeutic affect. It is even possible that the common denominator responsible for the improvement is, in fact, the personality of the therapist, and not the kind of treatment he applies. Habitual visual thinking is an exception in this respect: no "treatment" seems to influence it. This is hardly surprising, as the visual thinking is probably a constitutional peculiarity, thus being not amenable to any therapeutic endeavour.

6. CONCLUSIONS

1. "Thinking" in clear and vivid visual images, resembling silent films, seems to be normal in children and pre-literate human groups.

2. It probably persists, in a rudimentary form, in many artistic and creative adults even in our type of culture, though its complete survival in adults seems to be not only extremely rare, but frankly abnormal. However, in some rare cases it may represent the usual form of conscious, reality-testing, thinking, and may harmlessly "co-exist" with the common, verbal type of thinking. Usually the individual concerned remains entirely unaware of its existence.

3. Two aetiological hypotheses have been advanced: (1) visual thinking is a "fixation" at, a "regression" to, a less mature, pre-verbal type of thinking (a psychodynamical interpretation); and (2) visual thinking represents an individual peculiarity, which may be, up to a certain degree, constitutionally predetermined (a genetic interpretation).

4. This type of thinking seems to be related on the one hand to such para-hallucinatory visual experiences as eidetic imagery, day-dreaming, hypnagogic imagery, dreams, etc., on the other hand to the "ordinary" visual hallucinations.

5. A similar, but thematically usually very restricted, condition may sometimes occur in some cases of obsessional states. In such cases some mild obsessional traits may be traced out in the "pre-morbid" personality of the subjects concerned.

6. The treatment of these phenomena should be directed at the underlying, or accompanying, psychological disorder.

7. SUMMARY

The existence of an uncommon, in adults of our culture, type of thinking in terms of vivid visual images, i.e. of "*visual thinking*" was postulated. It was thought to be related to autistic thinking, to archetypal images, and to some similar phenomena, belonging to the vast group of "waking fantasies". The

phenomenology of "visual thinking" and of some other para-hallucinatory experiences was briefly sketched and illustrated by a few clinical cases. One of them clearly manifested a habitual way of thinking in visual images. On some occasions this would become obsessively perseverative, and then the patient would become aware of it. Some other illustrations (i.e. our cases "C" and "D") presented a typical picture of obsessional neurosis accompanied by a vivid obsessional visual imagery, precipitated by some emotionally over-valued, or traumatizing, ideas, or "fears". Certain aetiological hypotheses were put forward, and some suggestions regarding the possible treatment were made.

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THE MÜLLER-LYER ILLUSION IN SCHIZOPHRENIC PATIENTS*

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THE Müller-Lyer illusion is one of the best-known geometrical optical illusions. It was described by Müller-Lyer in 1889 (7) and first studied quantitatively by Heymans in 1896 (5).

Figure 1 illustrates this illusion:



FIG. 1.—Müller-Lyer figure used in the experiment.

Segments “a” and “b” are the same length (each 2 inches). However segment “a” which ends with two “arrow feathers” looks longer than segment “b” which ends with two “arrow heads”.

The literature on the subject of the Müller-Lyer illusion is very extensive and will not be reviewed in this paper. It is important to mention, however, that no significant correlation has been found between intelligence and susceptibility to this illusion (3), and also that there are no reliable sex or age differences in the sensitivity to it (4, 10). The latter case applies to adults only; in young children the age is important because as children grow older they become less susceptible to the illusion (10). Since it occurs not only in human beings but also in animals, it must be due to some basic property of the nervous system (11).

Boring (2) in his review of the subject mentions twelve theories which were put forward by the early investigators to explain the phenomenon. The majority stressed the importance of the “total impression” as the determinant of judgment. Others, such as Wundt (12), have stressed the importance of eye movement. However the subsequent finding that the illusion still occurs when the figure is exposed tachistoscopically for a fraction of a second casts some doubt on this latter explanation as there could be no effective eye movement in such a short interval of time. The Gestalt School of psychology explained the Müller-Lyer illusion and the other geometrical optical illusions as a particular instance of a more general principle of dynamic interaction of various

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parts of the visual field (6). The percept was not only determined by the particular stimulus, but also by the whole momentary visual field, which produced certain "forces" in analogy to an electric or a magnetic field. In the particular case of the Müller-Lyer illusion the "arrow feathers" would structure the whole visual field in such a way that "forces" will be produced which would "stretch" the perceived line. On the other hand, the "arrow heads" would structure the visual field in such a way that opposite "forces" will be produced which would "compress" the perceived line.

One can see that the Gestalt School threw its support on the side of the "total impression" theories of the early investigators. In spite of the wealth of theories there is not yet any certainty about the causation of this illusion. However it is obvious that the global type of perception, encompassing the whole field, as against the more analytical perception concentrating on the line itself to the exclusion of the "arrow feathers" and "arrow heads", is conducive to the enhancement of the illusion. Recent investigations showed that subjects who perceive more "analytically" on various visual tests are less susceptible to the Müller-Lyer illusion than are those who perceive more globally (8). Weckowicz and Blewett (11) showed that in schizophrenic patients there is correlation between size constancy, concept formation and the ability to perceive embedded figures. They put forward a hypothesis that in these patients cognitive process and, therefore, perception, is more global, less differentiated and less analytical than that of normal people. This is due to the fact that schizophrenic patients are not capable of shutting off information which is irrelevant to the task in hand. In the case of perception they are incapable of concentrating on one part of the visual field to the exclusion of other parts. They are therefore much more "field-bound", much more at the mercy of all the stimulation which comes from the environment than are normals. One of the deductions from this hypothesis is that schizophrenic patients are more sensitive than non-schizophrenics to those geometrical optical illusions which depend on the influence of the total visual field on one particular part, singled out for attention. The Müller-Lyer illusion fulfils this condition, so that schizophrenic patients should be more susceptible to it than non-schizophrenic controls. This paper reports the results of an experiment carried out to test this deduction from the major hypothesis.

METHOD

A set of fifty-six Müller-Lyer figures was used. Each figure was four inches long. The proportions of the two segments varied. There were four groups of fourteen figures each. The lengths of the segment between the "arrow feathers" in different groups varied by one-sixteenth of an inch from one and seven-sixteenths to two and four-sixteenths. In each case the length of the segment between the "arrow heads" was the remainder of four inches. The figures were drawn in blue ink on four by six inch white cards. The "arrow feathers" and "arrow heads" intersected the base line respectively at 150 degrees and 30 degrees. They were one-half inch in length. An additional card in which two segments were separated by a vertical short line served as a demonstration card. The cards were shown on a special small stand, which was completely covered by the card. The stand was always put at the same place on the table so that the position from which the figures were observed and the distance from the eyes differed only slightly from one presentation to another. To avoid changes in illumination, the cards were shown in artificial light (ordinary

electric bulbs) with the blinds drawn. The figures were always shown with the segment between the "arrow feathers" on the left side of the subject's visual field. The time of exposure was not controlled but the subjects were encouraged to give quick responses.* The cards were presented in random order. Before each experiment, the cards were shuffled. The subject was first shown the demonstration card and the experimenter explained to him what was meant by the longer and shorter segments. He was then instructed to tell each time whether the left or right segment was longer, or whether both were the same. He was told to use his first impression and he was encouraged to make his judgment as quickly as possible. After each judgment, a new card was put on the stand. Each subject was shown all fifty-six cards.

SAMPLE

The sample consisted of three groups. The first group was twenty-seven chronic schizophrenic patients. In all cases the diagnosis of schizophrenia had been firmly established by all psychiatrists who examined them. There were sixteen males and eleven females. Nine patients were diagnosed as hebephrenic, six patients as paranoid, two as simple, two as catatonic and eight as undifferentiated schizophrenics. The mean age of the schizophrenic subjects was thirty-eight years (range 25-55). No patient in whose case there was a possibility of mental deficiency or organic brain disease was included. Only patients who would co-operate in the experiment were included in the sample.

The second group was twenty-eight normal controls. They were members of the domestic and nursing staff of the hospital and some were voluntary visitors. There were seventeen males and eleven females. The mean age of the normal controls was thirty-five years (range 19-71).

The third group was nineteen non-schizophrenic patients. There were eleven males and eight females. Three patients were diagnosed as involutional melancholic, three as psychopathic personality, two as manic-depressive psychosis, three as alcoholic, three as epileptic, two as psychoneurotic and three were miscellaneous. Some depressives had undergone recently electric shock treatment. The mean age of the non-schizophrenic patients was thirty-five years (range 13-71). No subject with gross refraction error was included in the sample.

The subjects who used glasses for reading were instructed to use them in the experiment. Since there is no significant correlation between intelligence and susceptibility to the Müller-Lyer illusion (3) the samples were not matched for intelligence.

RESULTS

Subjects whose threshold for the Müller-Lyer illusion is low would judge the "arrow feather" framed segment longer than the other segment at smaller ratios of the two segments. On the other hand, subjects whose threshold for the illusion is high would require greater ratios of the two segments to make this judgment. (Ratio $\frac{a}{b}$ in Fig. 1). In this experiment the segment, framed by the "arrow feathers" was always on the left side of the visual field. Therefore the subjects in whom the illusion is produced by smaller ratios of the "arrow

* The time of exposure influences the susceptibility to the illusion (1). However, in all experiments where time is rigidly controlled, schizophrenic patients are usually penalized as they perform worse under stress conditions produced by timing.

feather" segments to the "arrow head" segments would judge the left segment longer more frequently than the subjects in whom the illusion is produced by greater ratios. The number of times the subject judged the left segment longer than the right segment was taken as his score of susceptibility to the Müller-Lyer illusion. In view of the fact that measurements could only be interpreted as having been made on an ordinal scale and not on an interval or ratio scales,* and in view of the fact that the variance of the scores of the schizophrenic group was much greater than that of the other groups, non-parametric statistics were used.

The median frequencies of "left longer than right" judgments for the three groups were as follows:

Schizophrenic patients	..	..	..	..	35.5
Normal controls	..	..	..	..	28.5
Non-schizophrenic patients	..	..	..	..	33.0

The statistical significance of the differences among the scores of the three groups was determined by ranking. The Kruskal-Wallis non-parametric one-way analysis of variance was performed on the ranks of the scores with the following results: $H=10.26$ (d.f.=2; $p<0.01$). This value of "H" shows that the three samples did not come from the same population as far as the sensitivity to the Müller-Lyer illusion is concerned. To test the difference in ranking between individual groups, the Mann-Whitney "U" tests were used. The results are summarized in Table I.

TABLE I

Groups				"U"	Z ¹
Schizophrenics vs. normals	..	..	..	159.5	3.69** ²
Schizophrenics vs. non-schizophrenics	..	..	..	172.5	1.89** ³
Non-schizophrenics vs. normals	..	..	..	166.5	2.16*

¹ Z is corrected for ties.

² Two asterisks denote $p<0.01$.

³ One asterisk denotes $0.05>p>0.01$.

DISCUSSION

The results show that there is a very significant difference in the susceptibility to the Müller-Lyer illusion between normals and schizophrenics and that there are less significant differences between both normals and non-schizophrenics and non-schizophrenics and schizophrenics. Schizophrenics are by far the most susceptible to the illusion of all the three groups. How can these results be interpreted? If there were no difference between normals and non-schizophrenics, the results would confirm the deduced hypothesis that greater susceptibility to the Müller-Lyer illusion is quite specific for the schizophrenic illness and is due to the peculiarities of the perceptual, and speaking more generally, cognitive processes of these patients. However, non-schizophrenic mental patients were found to differ from normals in the same direction as schizophrenics although to a lesser degree.†

* It is obvious that responses given to different ratios of segments cannot be regarded as equal units on a ratio scale. To use ratio scale on the data it would be necessary to give different weightings for smaller ratios and lower weightings for greater ratios.

† In order to check these differences by parametric statistics the average length of the "arrow feather" segment judged equal to the "arrow head" segment was found. In other words, the Point of Subjective Equality (P.S.E.) was calculated for each subject. The results obtained by analysis of variance were similar to those found by the previous method. However, in view of a lack of homogeneity of variance non-parametric statistics were considered more applicable to the data.

There are two possible explanations of this. The first, in our opinion less likely, is as follows: The susceptibility to the Müller-Lyer illusion does not depend on a specific diagnosis, but is a result of mental illness as such. Its cause could be explained as "emotional disturbance" or "regressive tendencies" of mentally ill people. However, this explanation, in order to account for the statistically significant difference between schizophrenics and non-schizophrenics, requires two assumptions. The first assumption is a positive correlation between the severity of mental illness and susceptibility to the illusion; the second assumption is that schizophrenics are more severely ill than other groups of mental patients. At the present, evidence in support of these assumptions is lacking.

The other explanation, preferred by the authors, is the following one: The samples used in the experiment were not homogeneous enough. In the sample of normal controls were included a few university students who worked as summer relief nurses. These subjects, although they denied it, could have been familiar with the Müller-Lyer illusion and could have artificially lowered the scores of the normal group. The statistically significant difference between the schizophrenic patient group and non-schizophrenic patient group is much more important. Thus the authors believe that two independent factors were responsible for the differences obtained. The first was a non-specific one, perhaps due to the fact that the normal control sample was not properly matched with the other samples. The second was more specific and was responsible for the difference in the sensitivity to the Müller-Lyer illusion, found between schizophrenic and non-schizophrenic patients. Schizophrenics are more susceptible to the Müller-Lyer illusion than non-schizophrenics. Thus a deduction from a more general hypothesis that perception and, speaking more generally, cognition in schizophrenic subjects is more global, less differentiated and analytical than that of non-schizophrenic subjects has been confirmed by the experiment. This shows that schizophrenics have difficulty in maintaining a perceptual set and in concentrating on one part of the perceptual field to the exclusion of other parts. In broader context it means that these patients are less capable of shutting off information which is irrelevant to the task in hand.

SUMMARY

Susceptibility to the Müller-Lyer illusion was tested in schizophrenic patients, non-schizophrenic mental patients and normals. A significant difference was found in the susceptibility to the illusion between the groups. Schizophrenics were more susceptible to the illusion than the other two groups. Non-schizophrenics were less susceptible than schizophrenics and more susceptible than normals. The significance of this finding for the cognitive process in schizophrenic patients was discussed.

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CLINICAL TRIAL OF "STELAZINE" ON APATHETIC CHRONIC SCHIZOPHRENICS*

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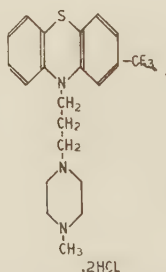
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INTRODUCTION

"STELAZINE" is the trademark name for Trifluoperazine. It is a derivative of phenothiazine with the following chemical formula: 10-3-(1-methyl-4-piperazinyl)-propyl-2-trifluoromethylphenothiazine dihydrochloride, or structurally:



Its pharmacological properties have been described elsewhere (3).

It suffices here to say that this drug has been found to be ten times more potent than chlorpromazine in blocking the conditioned escape response of animals to harmful stimuli. It has also been found to be more potent than chlorpromazine in depressing spontaneous motor activity in animals. Lehmann and Knight (10) have found by psychological laboratory techniques that in normal volunteers the drug acts selectively to decrease sensory and cognitive input and psychomotor speed and, at the same time, to increase attention, concentration and general vigilance.

The majority of the clinical trials reported in the literature are uncontrolled clinical studies. Only some will be reviewed here. Goldman (7) studied the effect of the drug in 500 mental hospital patients. He found it an effective antipsychotic substance. He described the following side-effects: Parkinsonism, dystonia, turbulence, allergic reactions, and mild autonomic reactions. Rudy, Rilandi, Costa, Himwich, Tuteur and Glotzer (12) reported on the basis of a controlled study that the drug produces improvement in acute and chronic psychotics to the same extent as chlorpromazine at dosage levels approximately one-tenth of those required of chlorpromazine. The side-effects

* Approved by the Saskatchewan Committee of Schizophrenia Research.

included: Parkinson-like symptoms, anorexia, weakness with impairment of gait and equilibrium. The blood pressure was not affected.

Brooks (2) reported that Stelazine is particularly useful with apathetic withdrawn chronic schizophrenic patients, because in contrast to other tranquillizers it activates these patients and makes them accessible to psychotherapy. Forrester (6) reported serious side-effects which prevented the drug from being used routinely.

Feldman (4) made a study of the side-effects of the drug. He enumerated the following: drowsiness, Parkinsonian symptoms, anorexia, weakness, dizziness, dermatitis, hypotension, depression, blurred vision. According to this author, these side-effects apparently resemble those of other phenothiazine derivatives, but they are less frequent and less severe. Freyhan (5) described the extrapyramidal symptoms, occurring as the side-effect of the drug and also their management. He described: Parkinsonism, dyskinetic syndromes and akathisia. He found that Parkinsonism can be controlled by anti-Parkinsonian drugs such as Cogentin or Kemadrin; dyskinetic syndromes by intravenous injections of caffeine sodium benzoate and akathisia by Kemadrin. Madgwick, McNeill, Driver and Preston (11) reported that chronic schizophrenics benefited from a Stelazine therapy and that some withdrawn patients became accessible and started participating in group activities. They also showed improvement on psychological tests of motor speed, co-ordination and attention level. The possibility that production of Parkinson-like signs could be used as an index of therapeutic potential has been studied by Karn and Kasper (9). These investigators using Stelazine and relieving Parkinsonism with Cogentin were unable to show any significant benefit from development of this side-effect as compared with the improvement shown by a group resistant to it.

PRESENT STUDY

Since violent, aggressive and hallucinated schizophrenic patients are usually well controlled by chlorpromazine and reserpine, the most difficult problem for therapy and management in chronic wards are apathetic, lethargic, withdrawn schizophrenic patients. They are often completely inaccessible to all attempts at socializing them and to psychotherapy. The reports that Stelazine activates such patients were considered, therefore, very important. The purpose of the present study was to find out to what extent apathetic, lethargic and withdrawn chronic schizophrenics would benefit from Stelazine therapy by becoming more active and accessible.

SAMPLE

Forty chronic schizophrenic male patients were selected from the same ward. The original diagnoses were: hebephrenic 15, catatonic 12, paranoid 3, simple 6, undifferentiated 4. However, at the time of the examination, all the patients presented a very similar clinical picture. They were apathetic, almost completely mute, withdrawn and disinterested in the environment. All of them showed extreme blunting of affect. All previous attempts with insulin treatment, electrical convulsive treatment, drug treatment, psychotherapy and group therapy had failed.

The sample included a pair of identical twins, who had developed schizophrenic illness within a few months and who presented identical clinical pictures*. After having been selected for the study the subjects were rated

* The potentiality of using identical twins for controlled drug studies is tremendous and largely unexplored.

with the Weyburn Assessment Scale by one of us (T.F.W.). This scale was constructed by Blewett and Stefaniuk for the purpose of assessment of chronic schizophrenics. Its reliability, validity and factor analysis are reported elsewhere (1). On the basis of this assessment the subjects were divided into two matched groups of 20. The mean score on the Weyburn Assessment Scale of either group was 60.7 (ranges 35-85, and 39-85). The mean age of either group was 46.2 years (ranges 64-36 and 64-34). The mean length of stay in the hospital was in one group 16.1 years (range 25.3-7.5), in the other, 16.7 years (range 28.7-5.7).

Thus one can see that the groups were almost perfectly matched as to the score on the rating scale, the age and the length of stay in the hospital. The previous medication was withdrawn for about two weeks before the patients were selected for the experiment. One of the identical twins was included in the first group, the other in the second group.

METHOD

The "Double blind" method was used. To establish the basic level of behaviour, both groups were put on placebo for three weeks. During that time the subjects were observed by the members of the nursing staff, who wrote down their daily observations. At the end of three weeks the subjects were rated again on the Weyburn Assessment Scale by the same rater. Following this, one group was put on the drug, the other continued on the placebo. The drug group started on 5 mg. Stelazine b.i.d., which was increased to 5 mg. t.i.d. after three days, and to 10 mg. b.i.d. after one week. For the next two weeks the subjects remained on 10 mg. b.i.d. The placebo group received the corresponding number of inert tablets. After three weeks of treatment the subjects of both groups were rated again on the Weyburn Assessment Scale by the same rater. The experiment was continued for another two weeks during which in the drug group the dose of Stelazine was increased to 30 mg. a day (in the subjects who did not develop side-effects). After that the final rating of both groups was carried out. One of us (T.F.W.) who rated the subjects, did not see them in between the rating periods. The other one of us (T.E.W.) saw the patients daily, adjusted the dose of medication and prescribed Cogentin to those subjects who showed side-effects.

RESULTS

In assessing the results the following points were taken into consideration: (a) the scores on the Weyburn Assessment Scale, (b) observations of the nursing staff, (c) follow-up study.

(a) *The Scores on the Weyburn Assessment Scale*

The mean ratings of the two groups are presented in Figure 1.

It can be seen by Figure 1 that Stelazine lowers the score on the Weyburn Assessment Scale. (Lowering of the score means improvement.) To test the statistical significance of this finding "t" tests were carried out in both groups of the mean differences between 1-2, 2-3, 3-4 ratings, and also between the mean of the ratings 1 and 2 (the ratings before the drug was administered) and the mean of the ratings 3 and 4 (the ratings after the drug was introduced).

The results are summarized in Table I.

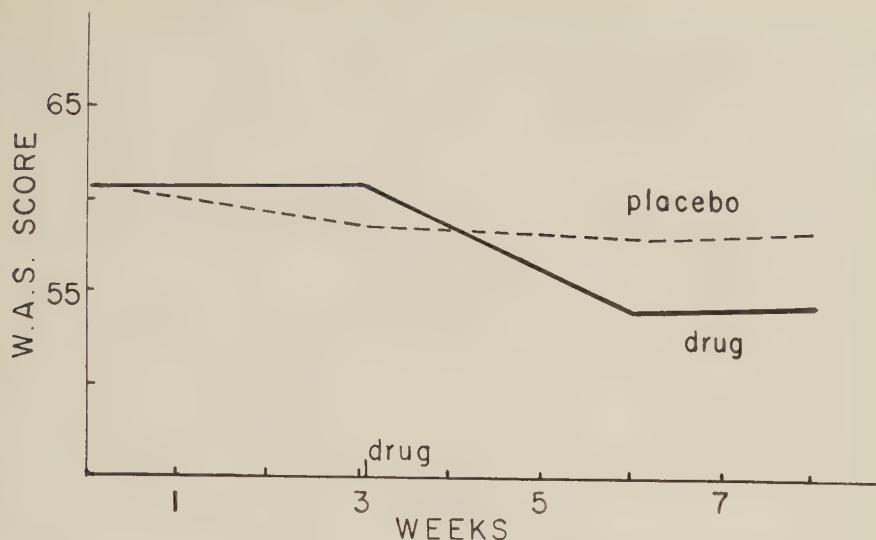


FIG. 1.—The mean ratings on the Weyburn Assessment Scale of the Stelazine and placebo groups on the initial assessment and also at 3, 6 and 8 weeks intervals.

TABLE I

Rating	Placebo Group			Drug Group		
	Mean Difference	S ²	t	Mean Difference	S ²	
1-2	1.8	44.06	1.176 (n.s.)	-.40	79.84	.195 (n.s.)
2-3*	.65	42.23	.436 (n.s.)	6.80	116.56	2.731 (.05 > p > .01)
3-4	-.50	64.25	.272 (n.s.)	-.45	33.05	.341 (n.s.)
1 and 2† 3 and 4 ..	1.10	29.76	.880 (n.s.)	6.38	71.35	3.289 (p < .01)

* Stelazine was introduced in the "Drug" group between the 2nd and 3rd ratings.

† The 1st and 2nd ratings (before Stelazine was introduced in the "Drug" group) and also the 3rd and 4th ratings (after Stelazine was introduced in the "Drug" group) were averaged for each subject.

One can see from Table I that administration of Stelazine lowers significantly the score on the Weyburn Assessment Scale.

The score of the Weyburn Assessment Scale consists of ratings of 23 items of behaviour. Factor analysis (1) has shown that from these ratings six factors can be extracted.

The first factor was related to the level of hospital care and to a deteriorative process resulting from living for prolonged periods of time in a "backward" environment.

The second factor was related to the degree of thought disorder.

The third factor was identified as having to do with the ability to relate to and approach other people.

The fourth factor was identified as a "motor" factor.

The fifth factor is related to unwillingness to speak.

The sixth factor is a factor of general cleanliness, which may be related to nursing care.

In order to find out which general areas of behaviour are influenced by the drug, the following procedure was adopted:

Only the second and the third ratings were used. (The 2nd rating was done immediately before the "Drug" group was put on Stelazine, the 3rd rating was done three weeks afterwards.)

Each individual item in the rating scale of each subject was multiplied by its factor loadings. By summing up these products factor scores were obtained for six factors for each subject. The significance of the mean differences between factor scores before and after the drug was introduced were calculated in both groups by "t" test.

The results are summarized in Table II.

TABLE II

		Drug Group		Placebo Group		
Factors	Mean Difference Between Scores	S ²	"t"	Mean Difference Between Scores	S ²	"t"
1st	.. 5.266	34.90	3.886†	1.570	11.34	2.03*
2nd	.. .370	5.44	2.183*	.374	1.10	1.55
3rd	.. -.113	.151	.565	.069	0.70	.51
4th	.. .926	.899	4.270†	.346	0.51	2.10
5th	.. .811	.723	4.160†	.671	1.25	2.61*
6th	.. .128	.152	.450	.370	1.54	1.30

* Significant at 5 per cent. level.

† Significant at 1 per cent. level.

It can be seen by Table II that in the placebo group only two mean score differences are significant at 5 per cent. level, while in the drug group three differences are significant at 1 per cent. level and one difference at 5 per cent. level. In the case of the third factor the differences in the two groups were in the opposite direction. The value of the "t" of the difference between the mean scores of the two groups on the second ratings is $t=2.110$, which is significant at 5 per cent. level. This means that on the second assessment the "drug" group had significantly greater ability to relate to and approach other people, than the placebo group. There was also a significant improvement in the drug group in the areas of behaviour related to the 1st, 4th and 5th factors. It means that the subjects in the drug group became less "deteriorated", more mobile and more willing to speak. There was a change in the same direction in the "placebo" group, but it was less significant.

(b) *The Observations of the Nursing Staff*

The nurses in the ward kept records of the subjects' behaviour. These records were analysed for the number of statements referring to improvement of the subjects. In the case of 18 subjects statements referring to their improved conditions were made of these 17 subjects who were receiving Stelazine and only one subject placebo.

The following are the examples of the statements made in the nursing records: "more co-operative, more sociable, more accessible", "more active and brighter", "more relaxed", "show more interest in work and activities", "converses more freely and logically", "neater in dress", "more cheerful", "fewer mannerisms", "tries to help with ward work", "less tense", "asked to have letter written home to his sister for money", "asked to go out with groups", "asked if he could go to wash his hands and face". All these observations indicate that the subjects became more accessible, less autistic, less tense and

more interested in the environment. To summarize: in the "drug" group 17 subjects showed some improvement, 3 remained unimproved; in the "placebo" group 1 showed some improvement and 19 remained unimproved. (The difference is so obvious that no statistical test of significance is needed.)

(c) *Follow-up Study*

At the conclusion of the experiment the patients who received Stelazine continued their medication for a further 70 days. In some subjects the dose was increased to 30 mg. t.i.d. At the end of this period marked clinical improvement was noticed in 6 patients. In general, the improvement noted was in disappearance of markedly asocial behaviour, such as gross negativism, surly or disgruntled attitudes; uncouth habits such as nose picking or eating material other than food. One 41-year-old patient who had been in hospital continuously since 1944, improved sufficiently in the eyes of both hospital staff and his relatives to allow him to leave the hospital on parole. He showed a disappearance of auditory hallucinations, became much less negativistic and became willing to converse with the staff and the relatives.

A similar remarkable change was seen in a 48-year-old nearly deaf man who was relieved of his paranoid delusions, coupled with great pressure and incoherence of speech so that he became friendly and quite comprehensible.

A 64-year-old intelligent man who previously had been quite negativistic and had had incomprehensible logorrhea, became a friendly but seemingly bewildered gentleman. The bewilderment was quite explicable, since this man had been a patient continuously for 27 years.

Finally, in no patient on the drug was a deterioration of the mental state noted.

SIDE-EFFECTS

During the experiment the following side-effects were noted: drowsiness, 8; muscular rigidity, 6; dizziness and unsteadiness, 4; feeling of malaise or weakness, 4; masklike expression, 3; excessive salivation, 3; tremors, 3; restlessness (motor), 3; shuffling gait, 2; pain in hips and shoulders, 2; excessive perspiration, 2; difficulty in swallowing, 2; muscular spasms, 1; difficulty in speaking, 1; overtalkativeness, 1; irritability, 1; sleeplessness, 1; incontinence of bladder, 1; excessive thirst, 1.

Thus one can see that the most frequent side-effect was drowsiness, followed by Parkinsonism. The latter was definitely present in 5 cases. Less frequent were side-effects such as muscular pains, difficulty in swallowing, muscular spasms and excessive perspiration which can be classified as dyskinetic syndromes. Also symptoms of "akathisia" (motor restlessness) occurred less frequently.

Parkinsonian syndrome was controlled quite well by Cogentin, 1 mg. per day. In one case of muscular pains, injections of caffeine benzoate (7.5 g.) were used with good results. The other side-effects could be controlled by reducing the dose of the drug. In no case did side-effects necessitate interruption of the treatment.

DISCUSSION

One can conclude that the overall results were as follows:

One patient was sufficiently improved to be discharged on parole, 2 patients showed marked improvement and 14 showed slight improvement, while only one patient improved slightly in the placebo group. In view of the fact that the

cases selected for the trial were "hopeless" cases, that the average stay in the hospital was more than 16 years and that many patients have been hospitalized for more than 20 years, the results are quite promising.

Stelazine appears to be a useful drug in the management of apathetic, withdrawn schizophrenic patients. It "activates" them and makes them more accessible to group therapy and psychotherapy. It is the experience of Weyburn Hospital that group activity (patients are members of small groups) is perhaps the best way to socialize chronic schizophrenic patients. Group activity, even if it does not "cure" the illness, prevents extreme regression, "deterioration" and disculturation, which used to be the fate of chronic schizophrenics permanently hospitalized in mental institutions. The most difficult patients from the point of view of group activity are those patients who are lethargic and withdrawn. Stelazine seems to be useful in these patients. They can be activated by this drug and then encouraged to participate in group activities. Thus they can be prevented from "deterioration" and in some cases, sufficiently socialized and rehabilitated to be discharged from the hospital under relatives' care.

One can speculate on the mode of action of this drug and why it is useful with chronic "lethargic" schizophrenics. Lehmann and Knight's (10) finding is very interesting in this connection. It will be remembered that these authors have found that in normal volunteers, Stelazine decreases the sensory and cognitive input. The fact that "lethargic" and apathetic schizophrenics benefit from this drug, suggests that these patients may be "overwhelmed" with sensory stimulation and irrelevant information and brought into a "standstill". (There are so many alternatives in the cognitive input that they cannot make a choice.) This would agree with the hypothesis concerning cognitive functioning in schizophrenic patients put forward by Weckowicz and Blewett (13) and also with Harris's (8) finding that the schizophrenic patients benefit from sensory deprivation.* The drug produces side-effects, many of which are quite unpleasant for the patients. The most important side-effect is Parkinsonism. However, it can be controlled quite well with anti-Parkinsonism drugs such as Cogentin, and also by adjusting the dose of Stelazine. This latter procedure seems to be effective also in controlling the other side-effects.

It is important that the physician in charge and the nursing staff should look for the early manifestations of the side-effects and deal with them at their early stages.

It is the feeling of the authors of this paper that the benefits accruing from Stelazine therapy outweigh the drawbacks of its side-effects. It is a useful adjunct in the management of apathetic chronic schizophrenics.

SUMMARY

1. A clinical trial of Stelazine was carried out in apathetic chronic schizophrenics.
2. "Double blind" technique was used with 20 subjects in the drug group and 20 subjects in the control group.
3. Both groups were matched as to the score on the Weyburn Assessment Scale, age and length of hospitalization. The groups included a pair of identical twins (one in the drug group, the other in the control group).

* The study of the effect of tranquilizers on perception may be helpful in arriving at a physiological and psychological model of schizophrenia. They appear to have an opposite effect on perceptual processes to that of hallucinogenes, such as LSD. The part of the nervous system involved is presumably the reticular activating system.

4. Stelazine was found to activate apathetic chronic schizophrenic patients and to make them more accessible to group therapy and physiotherapy.
5. The side-effects of the drug were described.

ACKNOWLEDGMENTS

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HYPNOTIC METHODS IN GROUP PSYCHOTHERAPY*

By

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AN outstanding problem with neurotics in the psychiatric out-patient clinic is that of coping with the pressure of numbers whilst continuing to afford an adequate degree of therapy. Views do evidently vary enormously as to what constitutes adequate therapy. Within the same clinic it is possible to find one psychiatrist habitually seeing neurotic patients at weekly returns, and another seeing comparable patients once or twice only. The higher frequency of interviews gravely limits the case load and is only slightly preferable to the other extreme in which the service provided is discouraging both the patients and home doctor. It might be agreed that if the symptoms which the patient first presents are thought capable of abatement, then therapy should be afforded through the clinic until some reasonable moderation of the disability is established and progressive. It is presumably also justifiable to continue clinic attention where such work may be expected to prevent or much to limit an otherwise certain deterioration.

Possibly most psychiatrists adopt a middle course and continue to see the mass of neurotic patients as clinic out-patients at intervals of some weeks or months, until it is evident that no useful further therapeutic contribution is being made—although such patients might be expected yet longer to attend their home doctor. The provision of such clinic service leads to a heavy rate of referral from the general practitioners and inexorably there persists the sense in the psychiatrist that he could, or should, offer more psychotherapy to his neurotics. In day to day psychiatric life such psychotherapy is excessively limited. Extensive psychotherapy is practicable with the occasional patient only. Another possibility is for the patients to be treated in assemblages, and group psychotherapy will become considered.

The almost total absence of sustained group work with out-patients evidently indicates some considerable difficulties. Much can be laid at the door of a lack of disposition to these procedures on the part of the individual psychiatrist, allied to absence of training, and to absence of conviction as to their therapeutic value. Many of the snags, however, probably lie in organizational problems. In the average out-patient clinic there is often shortage of secretarial help and shortage of space. To form and re-form groups and keep in contact with these out-patients is exacting. This is especially the case where group discussion is the aim, when it is needful for each group to be formed of the same individuals in a reasonable quorum on every occasion. The resistance to a discussion approach is in many patients high, requiring a lot of pre-selection and often resulting in erratic attendances. Such disincentives as these will readily disillusion a busy doctor more accustomed to

* A paper read at the Spring Meeting of the Royal Medico-Psychological Association at Newcastle, May, 1959.

finding always the next patient in the waiting room. When one adds to these trials the onerous demand upon the doctor, arising from the need to recollect complicated histories and their inter-relationships within the group, it is scant surprise that out-patient discussion groups are so rare.

The need for out-patient group psychotherapy remains, and this paper describes one form which has proved continuously feasible and therapeutically profitable. The basis of the work is the hypnotic approach. It is certain that greatly more patients are capable of fruitful therapy by hypnotism than many psychiatrists are at present disposed to admit. It is probable that many neurotics are more aided by hypnotism than by any other form of therapy and certain that they can often be at least as much so aided as by more complex psychotherapy. Nevertheless, hypnotism is clearly not a single panacea and its use for emotional illnesses is perhaps questionable when undertaken without psychiatric direction. It is invariably the case that the patient will profit by other psychiatrically orientated measures applied either contemporaneously with the hypnotism, or at other phases of therapy.

One type of out-patient neurotic does, in particular, offer a continued therapeutic challenge. This is the syndrome of free anxiety tension with phobic additions; more often encountered in women than in men. Such a syndrome may be not only distressful to the patient over long years and burdensome to her family, but it can also be severely disabling as, for example, in the fairly common panic form with a greater or less degree of disability in going out of the house unaccompanied. Men are encountered having serious limitations upon their travelling range or character of transport. Having used varieties of psychiatric therapies, I have found none more generally effective for these patients than the hypnotic approach conducted in a group setting.

All patients in these groups have been suffering from morbid tension as a common theme and invariably the major suggestions have been of confidence and relaxation given with indications of post-hypnotic continuance and reinforcement. Some two-thirds of the patients have had varied phobias as major symptoms, but in general no specific suggestions have been thence aimed. Broadly it has been accepted (and in practice transpired) that these individual symptoms would take care of themselves. However, there have been symptoms such as stammer or eczema, which have been additionally approached by introducing appropriate suggestions such as clarity of diction, or coolness of skin and so on, which suggestions are not bizarre for other members of the group. A wide variety of such additions in suggestions have been made, but one is unconvinced that they offer any extra advantage over the simplest, broadest approach. Some symptoms could not be specifically alluded to in the group, such for example as sexual problems or enuresis.

The work has been in progress for nearly two years. Sessions have always been with the same therapist. They are held once each week in an evening, when the waiting room is free for these patients to congregate and chatter. A system soon developed of taking three successive groups of six. The number six was determined by the size of the consulting room, but it happens also to be suitable for observation of the patients. Seating is in reclining chairs in front of the therapist. Lighting is by reflection on the background ceiling to avoid an overhead glare. The patients are told to fixate on bright spots (which are produced by sticking milk bottle tops to the walls). The induction is in general unchanged from session to session, but is constantly adjusted in detail to suit the circumstances of the various patients both in their rate and degree of induction, and in relation to their symptoms. Everything is made as informal as

possible. The usual themes of increasing relaxation, drowsiness and calm are reiterated by intoning. Suggestions of eyelid heaviness and of limbs and face drooping continue, and intensification of the hypnotic state is pursued with such extent of emphasis as any given group response may indicate. In practice the group effects vary little, but newly-introduced patients may sometimes conveniently be "contracted out" early in the course of the first two or three sessions, by the use of some pre-arranged hand signal. It has been very usual to find that all six will enter stages of the hypnotic state and stay therein uneventfully. The unceasing pressure of loud hospital noises can be troublesome but most patients are quickly unmindful of this nuisance. Rarely a patient will fully awake during a session and this may call for closure; or, again by a hand signal, the patient is left out for the remainder of the session. Normally all patients awake within seconds of each other on the appropriate terminating request, but a person hard of hearing has sometimes needed a further louder command whilst the rest have already awakened.

The duration of hypnotic procedures with each group is up to 15 minutes. Also, on frequent occasions, a general group conversation is stimulated to last 5 to 15 minutes before the induction. This conversation is in effect a therapeutic group discussion which commonly springs from topics connected with the hypnotic procedures and responses. Patients are encouraged to ventilate their difficulties or qualms about the hypnosis. It is then found that other members will afford invaluable support. It happens over and over again that new patients are dubious as to whether they will be able to respond, but become then encouraged to hear from others of their similar earlier misgivings and how these became displaced by success. Often also a like aid will emerge to help some patients past that stage sometimes experienced in which, after a few initial sessions of increasing effect, a panic then arises on the patient sensing the lessening of their wilful control. However, now and again, a patient having experienced such a panic then finds it impossible to accept further sessions.

The procedure is simple and relatively brief in application. Organization is of manageable degree. It does not matter if all patients do not turn up at a session, nor does it matter which individuals compose any given group. The composition of the groups is totally flexible, patients simply being taken in from the waiting list as vacancies arise. At later stages of treatment it has been convenient to pair off some patients, who then attend alternating with each other, so receiving a halved rate of treatments. It is not necessary to preface a group hypnotic approach to any patient by individual hypnotic sessions (though this has happened with a few). A general explanation of the approach is given to each personally when the suggestion of such treatment is first raised, and beyond that the patient simply enters straightway into any group. The groups are composed of people at all stages of progress and number of attendances.

My impression is decidedly that the majority of the patients chosen for the group have done better or as well as would have been expected with an individual hypnotic approach. There are, of course, some patients one prefers, or has to, treat individually. Such, for example, as those who are "home bound" by a phobia, or who may require some very special procedure, such as an individually orientated suggestion, or where speed is needed. Two patients had a terminal two individual sessions immediately subsequent to a series of group approaches for the purpose of clearing up a residual symptom.

Some 70 sessions have been held, starting with one group, quickly rising to two, and becoming three groups from the twelfth session to date, with attendance averaging about 15 persons an evening. Some 65 patients have been

involved. The number of treatments expressed as for individuals is around 750—an indication of the volume of therapeutic work attainable by this method. Detailed records of responses, reactions and results have been kept. Patients have also answered a very full questionnaire. Responses are estimated during each session by the therapist and rated in five grades coded as 0 to XXXX. Forty patients entered very satisfactory degrees of the hypnotic state in which upward of 60 per cent. of all their responses are noted as XXX. Where the hypnotic response occurred this was clearly evident with most patients within three sessions, often at the first session, but occasionally not until the 5th or 6th.

Absence of any perceptible degree of hypnotic response has occurred in about three patients, but responses not thought to be adequately consolidating with progressive attendances have in some seven further cases led to advice to discontinue at fewer than ten treatments. Absence of adequately deep response has usually been linked with absence of therapeutic resultant; but in a very few instances responses thought adequate at numerous attendances have failed to become associated with commensurate clinical improvement. About 10 of the patients lapsed of their own accord, usually within 5 sessions—almost all of whom had shown evidence of satisfactory hypnotic responses. Out of the total of 65 patients, around 20 have therefore either been early discontinued or have prematurely lapsed.

Although adequate improvement has eventuated with several in less than some 12 attendances, most of these patients would appear to require at least 20, and a few have warranted extension to 25 or even more (at which point they have usually entered alternating pairs).

Some 56 patients were sent questionnaires; all 56 had also been reviewed at follow-up appointments. Others were left out as being at too early a stage of treatment or of unknown location. Within the 48 repliers, 16 might be reckoned as having a “very good” result; 9 as “good”; 10 as “moderate” and 12 as unaltered. In the 8 non-repliers, one could be counted as having a “moderate” result, the other 7 as unaltered. In round figures it can be said that about one quarter give a very good clinical result, about a further quarter give a worthwhile result, and about a half are very little or not at all aided.

When a result has been assessed as “very good” this means that so far as feasible the outcome has been judged to be notably better than could have been expected with any other practical form of therapy. Some other therapies, such as drugs and occasional psychotherapeutic individual interviews were at the same time being used by the same therapist with all these patients. The ratings of results are of improvements thought wholly due to the group hypnotic approach; that is improvements additional to such as could reasonably be ascribed to other therapies used at the same time.

No difficulties of any kind have emerged. No patient has ever created any disturbance within a group. Indeed the absence of spontaneous abreactions suggests that there is restraint dependent upon a continued awareness of the presence of other patients. This does not seem in practice to lead to any loss in therapeutic effectiveness. The communal ritual of group hypnotherapy heightens the sense of companionship and the cheerfulness of the dispersing group is always perceptible. No patients raised any objection to being treated in a group, although quite a lot in their written replies expressed the idea that they might have done better if treated alone. The impression of the therapist is that no clear reason existed in the majority of these cases why they should, in fact, have done better if treated individually; but some might have done so. Some half of

those patients giving relevant replies on the point stated that being in a group offered advantage to them.

Increasing facility in the tolerance of emotional charges is evidenced through the accounts of several patients. Various panic reactions have been described in the early sessions just after hypnotic response had begun to be established. The subsidence of these panic reactions in the succeeding sessions would seem then associated with accelerated clinical improvement. It should be added that these panic evidences are not readily observable to the therapist during treatment, although if a patient has mentioned such happenings then their occurrence may be guessed at in subsequent sessions through observation of slight indications in bodily movements. About six patients in answering the questionnaire referred to sensations of "sinking" or of being about to fall into a "black pit" (which was, of course, never suggested to them). Those giving these references are predominantly patients who came to notable improvement. They also seemed to feel that if they could only entirely get over this sensation of the "blackness" and the apprehension they had felt about it, which they sense has limited their hypnotic response, that then they would be even more well. Actually the mass of patients experienced no panic, though minor degrees of apprehension are common enough in the early stages of treatment.

No patient was worsened, nor did any come to any disadvantageous results. There has never been any trouble in taking people off treatments at the end of a course. With those patients who became notably benefited, there has been no evidence of diminution of this benefit subsequent to ceasing treatments. Once again, the old bogies about hypnotic therapy are found baseless in practice.

SUMMARY

No difficulties have arisen in a two-year continued experience of out-patient group psychotherapy using a hypnotic approach.

Patients are taken weekly in groups of six, several groups at a session. All have been chosen as having undue tension as their common feature, most have phobic states, a few have more specific difficulties, such as stammer, tic, or eczema. They come from the clinic practice of the group therapist and are over the same period treated also by occasional psychotherapeutic interviews and medication.

Estimates of the efficacy of group hypnotherapy are as of degrees of improvement extra to that which could reasonably be expected from these other aids. Of all starters a quarter give a very good clinical result, a further quarter give a worthwhile result, the rest are very little or not at all aided.

THE MECHANISM OF THE COMBINED TREATMENT OF DEPRESSION WITH IPRONIAZID AND RESERPINE

By

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THE beneficial effect of monoamine oxidase blockers on depressive states has been established. Their therapeutic effect has been assessed at ranging between 60 and 80 per cent. of all cases treated. We have tried to improve on this rate by combined treatment with iproniazid and reserpine, a combination which has been used in experimental animals by Chessin *et al.* (1, 2) and Brodie *et al.* (3). The results of our treatment will be briefly described in this paper.

MATERIALS AND METHODS

The doses of iproniazid given ranged between 50 and 200 mg. per day, and those of reserpine between 1 and 4 mg. A total of 39 cases of depression were divided into three groups, the first group—14 cases—receiving iproniazid alone, based on earlier experiences of Kaffman and Winnik (4). The second group, consisting of 13 patients, started with iproniazid followed by reserpine 21 days later. The third group, numbering 12 cases, underwent simultaneous treatment with iproniazid and reserpine right from the beginning. In all three groups, treatment was preceded by examinations of E.C.G., blood count, haemoglobin, blood sedimentation rate, plasma albumin and globulin, free and esterified cholesterol, and liver function tests. In addition, we studied twice weekly the urinary excretion of FSH and blood ACTH (Sulman, 5) and daily the urinary excretion of 17-KS and 17-OH, in order to detect any endocrine changes provoked by the treatment.

RESULTS

Group No. 1, which received daily doses of 100–200 mg. iproniazid for 4–6 weeks, showed a recovery rate of 65 per cent. (Table I). Later the patients could be kept on smaller maintenance doses.

Group No. 2 received varying doses of iproniazid (Table II) to which was added, after 21 days, reserpine at dose levels of 3 mg. daily during the first

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7 days and 4 mg. daily during the following 14 days. Treatment lasted 6 weeks
in all and was followed later by smaller maintenance doses. This group had a
recovery rate of 70 per cent. (Table III).

TABLE I
Results of Treatment with Iproniazid Alone (Group 1)

Diagnosis	Total Number of Cases	No Change	Improved
Endogenous depression	4	2	2
Involuntional psychosis	7	1	6
Schizo-affective psychosis	3	2	1
Total	14	5	9=65%

TABLE II
Dosage Schedule of Iproniazid (Group 2)

Day of Week	1st Week (mg.)	2nd Week (mg.)	3rd Week (mg.)
1	50	175	200
2	75	175	200
3	100	175	200
4	125	175	200
5	150	175	200
6	150	175	200
7	150	175	200

TABLE III
Results of Treatment with Iproniazid and Later Addition of Reserpine (Group 2)

Diagnosis	Total Number of Cases	No Change	Improved
Endogenous depression	3	1	2
Involuntional psychosis	9	2	7
Schizo-affective psychosis	1	1	—
Total	13	4	9=70%

Group No. 3 had the two preparations administered simultaneously. The
patients received 50 mg. iproniazid 3 times daily and 1 mg. reserpine daily at
bedtime for 4–6 weeks. They showed a recovery rate of 75 per cent. (Table IV).

TABLE IV
Results of Simultaneous Treatment with Iproniazid and Reserpine (Group 3)

Diagnosis	Total Number of Cases	No Change	Improved
Endogenous depression	8	2	6
Involuntional psychosis	4	1	3
Total	12	3	9=75%

While the rate of improvement in the three groups was fairly even (65 per
cent., 70 per cent., 75 per cent. respectively), the clinical effects obtained with
the combination of iproniazid and reserpine were much superior to those

reported on the administration of iproniazid alone. The beneficial influence of reserpine became evident not only in an improvement in the general depressive state, elimination of the typical tension and sleeplessness, but also in a considerable reduction in side-effects which may develop during the first weeks of concentrated treatment with monoamine oxidase blockers. In all three groups improvement could only be detected after 2-4 weeks of treatment, and in none of them were there any complications.

Laboratory findings showed the following changes due to the treatment:

1. A marked tendency towards a decrease in the protein content of the plasma and haemoglobin during the second and third weeks, normal levels re-appearing in the fourth week;
2. FSH, which showed increased levels in 50 per cent. of the cases before treatment (urinary excretion of 50-200 RU/1), reverted within three weeks of treatment to normal levels (25 RU/1), a finding which was invariably a concomitant of a general improvement in the patients' condition.

Blood ACTH, urinary 17-KS and 17-OH excretion were not affected by the treatment. There was an increase of 4-6 mg./24 hours of 17-KS and 17-OH excretion during the first days of treatment which soon receded.

DISCUSSION

Mechanism of Effect of Iproniazid

The beneficial and synergistic effect of the combined iproniazid and reserpine treatment is against expectation and requires some explanation. We feel that the effect of the monoamine oxidase blockers could be explained by the blocking of an acceptor and enzymatic site on the surface of the cell, preventing destruction of catecholamines and serotonin. This mechanism would explain the optimal utilization of catecholamine and serotonin in the brain of patients to whom monoamine oxidase blockers have been administered. In Figure 1 the zero-line shows the structure of such a site, adapted to the special structure of noradrenaline (line 1) and adrenaline (line 2) respectively. This acceptor and enzymatic site is, however, not specific in all its 4 active patches. Thus, e.g., the first active patch may react not only with the phenyl but also with the indole group. This possibility is shown in line 3, where serotonin replaces the catecholamines. Another example of the limited specificity of this acceptor and enzymatic site is demonstrated in line 4 where iproniazid is inserted, its adherence to the active patches Nos. 1 and 4 blocking the monoamine oxidase. Line 5 shows that phenethylhydrazine (Phenelzine, Nardil) fits well into the same structure. The same holds true for phenisopropylhydrazine (Catron, JB 516)—line 6, for phenylcyclopropylamine (SKF 385)—line 7, for nialamide (Niamid)—line 8, and for isocarboxazid (Marplan)—line 9.

Imipramine (Tofranil) does not belong to this group of substances as its structure resembles that of chlorpromazine and is apparently connected with the structure of a hitherto unknown mediator of the central nervous system which may, in one case, provoke stimulation and, in another, depression, depending upon the mesencephalic cells affected. This would explain why relatively so similar substances as imipramine and chlorpromazine may exert such diametrically opposed effects.

Mechanism of Action of Reserpine

Reserpine liberates serotonin from certain parts of the brain since its chemical structure may permit an anti-metabolite effect towards serotonin

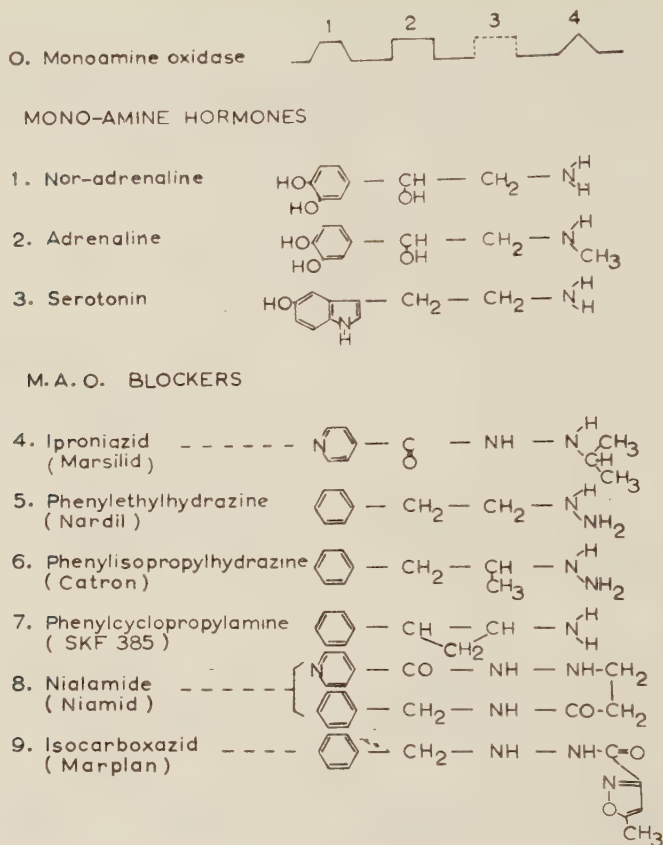


FIG. 1

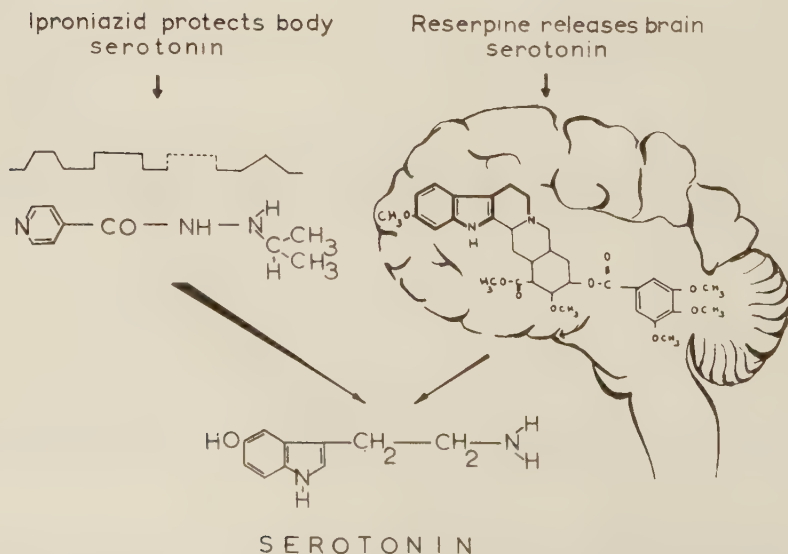


FIG. 2

(Fig. 2). Thus the synergistic and augmentative effect of reserpine on the monoamine oxidase blocker treatment may be explained by 2 mechanisms:

- (a) lower destruction and better utilization of serotonin and catecholamines following monoamine oxidase inhibition, and
- (b) additional liberation of brain serotonin.

Mechanism of the Endocrine Effect

The beneficial effect of the combined monoamine oxidase blocker + reserpine treatment on FSH secretion may be explained by the suppression of FSH production through reserpine. Such an effect in animals has been described by Khazan and Sulman (6). The site of this action lies apparently in the hypothalamus, at the centres which produce a gonadotropin-releasing factor acting via the anterior pituitary lobe.

Improvement of Therapeutic Results

It should be stressed that the beneficial effect of the combined iproniazid-reserpine treatment does not necessarily increase the percentage of recovery. We do not consider that the 75 per cent. recovery rate obtained with the combined treatment is much superior to the 65 per cent. rate obtained with iproniazid alone. However, there is one obvious improvement resulting from the combined treatment: the easier state created in the patient, the alleviation of sleeplessness and tension created by iproniazid. This is due to the beneficent effect of reserpine. In brief, reserpine is a synergist to the anti-depressive effect of iproniazid and an antagonist to its unwanted side-effects.

Side-effects observed in the first group (iproniazid alone) were, in order of frequency: vertigo, hypotension, dysurea, speech disturbances, constipation, paraesthesia and slight ataxia. In the second group (iproniazid followed by reserpine) these side-effects were noticed only during the first three weeks of treatment with iproniazid and they disappeared when reserpine was added. In the third group (iproniazid and reserpine given simultaneously) none of these side-effects were observed.

Maintenance

As a rule, after 6 weeks of treatment, a gradual decrease in the dosage of iproniazid was possible. The maintenance dose should be 50–75 mg. per day, distributed in two dosages given in the morning and following the afternoon nap. The maintenance dose for reserpine is 0.25–0.5 mg. per day which should be given in one dose at bedtime.

SUMMARY

Thirty-nine cases of depression are described in which treatment with iproniazid and with iproniazid combined with reserpine resulted in a 65 per cent.–75 per cent. recovery rate. The simultaneous administration of iproniazid and reserpine is superior to the treatment with iproniazid alone or the successive treatment with the two drugs.

The mechanism of action of iproniazid and other monoamine oxidase blockers is explained by the blocking of an acceptor-enzyme group common to serotonin and the catecholamines, which has 4 active patches corresponding to the aromatic group, C₁, C₂ and the amine group. We have also discussed the possible mechanism of action of the combined treatment and concluded that it is due to the increased liberation of serotonin. The combined method

considerably improved the depressive state within 2-4 weeks and completely did away with the side-effects observed during the treatment with iproniazid alone, especially sleeplessness and tension.

In cases with increased urinary FSH excretion, the combined treatment brought FSH levels down to normal within three weeks. Urinary 17-KS and 17-OH values increased during the first 3 days of treatment but soon returned to normal. Plasma protein and haemoglobin values were lowered in the first 3 weeks of treatment but later became normal.

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CLINICAL AND ENDOCRINOLOGICAL EFFECTS OF HYDROXYZINE

By

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In earlier papers we have shown that ataraxic drugs whose main point of attack lies in the hypothalamic area are able to evoke endocrine effects (1, 2, 3). These are obviously the result of depression of the reticular formation and hypothalamic centres responsible for the anterior pituitary's endocrine activity.

The formula of hydroxyzine (Fig. 1) reveals both anti-histaminic and tranquillizing properties. It is, however, the clinical consensus and also our experience that its tranquillizing effect alone is of little value in schizophrenic and endogenous psychotic disturbances. In 24 patients suffering from severe psychotic conditions with excitement we could not obtain improvement by doses up to 1,200 mg./d. We therefore studied the clinical and endocrine effects of hydroxyzine in 6 selected patients, 5 with neurotic conditions and 1 suffering from psychosis. The patients received doses from 3×25 mg. up to 2×250 mg. hydroxyzine in tablets and injections.

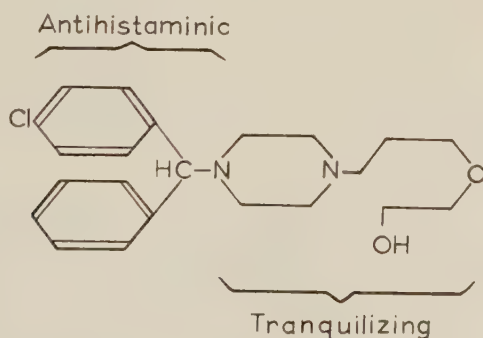


FIG. 1

TECHNIQUE

The patients were hospitalized for control without administration of drugs one week before treatment, when general blood and urine tests as well as endocrine examinations were carried out daily. The latter included determination of: FSH in urine (4), ACTH in blood (5), total oestrogen in urine (6), 17-KS in urine (7), 17-OH in urine (8).

RESULTS

Table I shows that of the 5 neurotic patients, 3 improved considerably (+), 2 improved while under treatment ($\pm$), while 1 psychotic did not react.

Results of the endocrine follow-up generally coincided with the clinical effect of treatment. Thus 17-KS excretion decreased considerably in patients Nos. 1, 2, 3, 5, 6 who responded well to treatment, whereas it rose in case No. 4 which did not respond. Excretion of FSH, oestrogen, ACTH and 17-OH was not affected.

As the patients were exclusively female, the effect on 17-KS excretion may safely be ascribed purely to their adrenal function. When the patients entered hospital their 17-KS excretion was invariably high, ranging between 6 and 22 mg. daily. During treatment there was a marked trend towards lower 17-KS excretion, especially in patients who became less agitated. This decrease appeared in most cases as early as 2 days after starting treatment, but became obvious only after 14 days with values between 2-8 mg. per day.

DISCUSSION

The relationship between 17-KS excretion and mental disturbances was thoroughly studied by Hoagland, Pincus *et al.* (9), and Reiss *et al.* (10). Decreased 17-KS excretion with normal 17-OH values during treatment with ataraxic drugs is very common and has been shown by us in patients who received chlorpromazine (1, 2) and reserpine (11). We ruled out the possibility that this decrease is due to hydroxyzine or its metabolites interfering with 17-KS delineation as follows:

1. Addition of 1 mg. hydroxyzine hydrochloride to 1 ml. urine did not change the 17-KS value of the urine.
2. Cases which did not react to hydroxyzine treatment showed no decrease in urine 17-KS.
3. Cases which reacted well to hydroxyzine treatment showed decrease of 17-KS excretion not immediately after starting treatment but only up to 14 days later.

Lower 17-KS excretion may thus safely serve as an indicator of the tranquilizing effect. Moreover, we could note that this decrease was clinically significant. Its prognostic value, however, depends on the nature of the disease and continuation of treatment.

The decrease of 17-KS excretion in the presence of normal 17-OH values clearly points to the lack of any detrimental effect of the drug on adrenal function. Such a decrease is a common experience in cyclothymic patients who pass from their depressive phase into the manic one and is the expression of psychic stress only. It is related to the activity of the zona reticularis of the adrenal, whereas 17-OH excretion is related to the zona fasciculata. The dissociation of the activity of both zones is a common experience, e.g. in Cushing syndrome where 17-KS values remain normal, while 17-OH values are considerably increased.

SUMMARY

The effect of hydroxyzine was studied in 6 patients with various psychological disturbances, ranging from hysteria to melancholia, anxiety, depression, phobia and conversive reactions. Generally this drug has a tranquillizing effect but is not sufficient for treatment of psychotic conditions. Thus one psychotic

TABLE I
*Effect of Hydroxyzine Treatment in 6 Female Patients
Hormone Excretion is Given as the Average of Daily Examinations Carried Out Throughout Whole Period of Treatment*

No. of Patient	Main Symptoms	Diagnosis	Daily Dosage Hydroxyzine (mg.)	Duration of Treatment	Effect of Treatment	17-KS mg./d		17-OH mg./d		Total Estrogens IU/d		FSH RU/d		ACTH Frog U/L	
						Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
1 I.L.	Anxiety tremor, vertigo, diarrhoea	Anxiety and convulsive reaction	75	20	+	13.2	6	10	9	50	50	<50	<50	<50	<50
2 H.H.	Depression, tremor, tachycardia, insomnia	Depression and convulsive reaction	125	30	±	13	5.7	7	8	25	25	<50	<50	<50	<50
3 R.A.	Anxiety, diarrhoea, tachycardia, panic	Phobic and anxiety reaction	125	30	+	16.8	5.4	8	9	20	20	<50	<50	<50	<50
4 B.L.	Guilt feeling, suicidal drive, insomnia	Agitated depression	250	50	—	12.4	17	11	10	10	10	<50	<50	<50	<65
5 M.W.	Hypochondria, insomnia	Agitated depression	300	25	±	6	4	11	8.2	20	20	<50	<50	<50	<50
6 M.D.	Phobia, hypochondria, insomnia	Phobic and anxiety reaction	500	30	+	16	8	6.9	5.7	25	25	<50	<50	<50	<50

patient did not respond. In minor disturbances, mainly neuroses, hydroxyzine may be considered efficient. All responding patients showed marked decrease of 17-KS excretion pointing to the tranquillizing effect of this drug. No other decrease in endocrine activity was noted: 17-OH, ACTH, as well as oestrogen and gonadotrophin excretion remained unchanged.

ACKNOWLEDGMENTS

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FACTORS RELATED TO THE OUTCOME OF DEPRESSION TREATED WITH E.C.T.

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THERE are two stages in the evaluation of a new treatment: the first is to determine if it has any effect at all, and the second is to determine as strictly as possible, the conditions of its applicability. In practice, these two stages overlap considerably, for they are not completely distinct. As soon as some evidence is available that a treatment is effective, attention tends towards ascertaining the precise indications for its use, the evaluation of its effectiveness, its contraindications and complications.

In the case of E.C.T., psychiatrists have a form of treatment which is recognized to be effective and has few contraindications and complications. The main indications for its use are now fairly well recognized: it has a definite but limited use in the treatment of schizophrenia; it is most effective in the endogenous depressions, and in the case of the involutional depressions it has radically transformed the prognosis. Nevertheless, there are still many difficulties in the use of electroshock as a treatment for depressive states. Unexpected failures to respond to it still occur, and these cannot be considered to be counterbalanced by unexpected successes. A particular attack of depression may not respond to E.C.T. at one stage, but will do so at another; and without a history of previous attacks to guide the therapist, there is no way of determining the "sensitive" stage beforehand. Finally, the relapse rate after treatment is high.

There have been many studies on factors related to outcome after treatment, but although much has been achieved, the situation is still unsatisfactory. The problem has become urgent since the introduction of iproniazid, imipramine, etc., for the treatment of depressions; for not only do these problems require solution in the case of the drugs, but in addition, the relative merits and indications of these two types of treatments now require investigation.

The evaluation of "prognostic" factors is not easy. The greatest stumbling-block lies in the nature of the group of patients used for the evaluation. Narrow selection in one variable eliminates its effect. For example, if age affects prognosis, its influence will be diminished if the range of the patients' ages is small and will disappear if all the patients are of the same age or thereabouts. Selection can occur in all sorts of ways: thus patients select themselves when they go to their general practitioner, and he selects from among them those he sends to the consultant, and so on. In the end, the

problem of evaluation is one aspect of the general one of drawing inferences from a sample to the population from which it is derived. In the present case, additional problems arise from the difficulty of assessing the outcome of treatment and the factors investigated.

This paper describes an attempt to deal with these problems by quantifying, as far as possible, all the relevant factors. Some are always thought of in quantitative form, e.g. weight, blood pressure, length of illness. Others have been quantified without difficulty, e.g. the use of a rating scale for assessing the patient's mental state; and finally, where this has been too difficult, the factor has been categorized into present, absent and doubtful.

POPULATION

The 49 men of this study were all in-patients who had been admitted to hospital with a depressive illness, and who, it was thought, would benefit from electro-convulsive treatment. They had been admitted because of an attempted or seriously threatened suicide, or because they were so depressed that it was considered unsafe to treat them as out-patients. A few were admitted because of suspected or confirmed physical illness which required hospital treatment before E.C.T. could be given. On aetiological grounds only, 20 were diagnosed "Endogenous Depression", as no relevant precipitating factors could be elicited, although there might be some doubt about this in the case of 9 of them. "Reactive Depression" was diagnosed in 29, but the relevance of external stress might be queried in 11 of these.

The mean age of these patients was 51.7 years ± 12.0 Standard Deviation (range 21 to 69 years). The mean length of the current illness was 12.7 months (range was 1 month to 10 years, although only 9 patients had a history longer than 10 months). Other items of information will be mentioned at appropriate points.

METHOD

Each patient was assessed by means of a rating scale (Hamilton, 5) on which ratings for 17 symptoms were made. In three additional ones positive findings were so infrequent, that they were excluded from the rating score total and considered separately. The technique of double assessment was carried out in all cases, both authors being present at each interview and independently rating the patient. The sum of both assessments was taken as the score for the patient. In addition to this, a detailed clinical and social history was obtained from the patient, supplemented by information from his relatives. The patient's weight, height and chest width were measured, and finally a Funkenstein test (mecholyol only) done. Owing to pressure of other work, this could be done on 38 patients only.

The patients were then given a course of E.C.T. The usual course was 6 treatments, but in a few cases, the course was discontinued at 4 or 5, because the patient refused to continue, became euphoric or confused. In a small number of patients who were resistant to treatment, the course was extended to a maximum of 10 treatments, or a shorter course repeated after a period of rest. Temporary remission with rapid relapse occurred in 14 patients, who were given another course, and then improved.

Patients were then assessed at least one month after the end of their course of treatment. It was not possible to see them all at a fixed time after treatment, as some patients were reluctant to attend, others had changed their address, and so on. Some only returned for reassessment because they

were beginning to relapse. These received a second course of treatment and were again assessed. A number of patients were assessed on two occasions, and nearly all of them have been followed up over a continuous period up to nearly 2 years. Where two post-treatment assessments were available, the "final assessment" was that one which most resembled the patient's continued state.

RESULTS

1. *Clinical Results*

The 49 patients studied form part of a group of 68 consecutive admissions, of whom 4 could not be seen for follow-up, although we heard indirectly that they were well. Of the remaining 15, one died of broncho-pneumonia and one committed suicide before final assessment. The other 13 did not receive E.C.T.; 5 of them refused it, 5 were not given it because of their physical state and 3 showed signs of spontaneous recovery before it could be started.

On the basis of clinical judgment we can rate the improvement of the patients and compare the result obtained with and without E.C.T. The results can be seen in Table I, and it is evident that those treated with E.C.T. have done much better than the others. It is not legitimate to test these figures statistically as the two "treatment groups" were not randomly selected.

TABLE I
Clinical Outcome

		Recovered and Improved	Unchanged and Worse	Died	Suicide	Total
E.C.T. ..	..	43	6	1	1	51
No E.C.T.	..	6	4*	1	2	13
Total	..	49	10	2	3	64

* One of these recovered spontaneously, relapsed and recovered after E.C.T.

2. *Clinical Syndromes*

The patients can be classified on aetiological grounds into Endogenous, Doubtful Endogenous, Doubtful Reactive and Reactive Depressions. Table II shows that the mean initial score of these groups diminishes in that order, which is in accordance with clinical experience. The mean final scores differ significantly but this is due to the high final score for the Doubtful Endogenous group. The differences between the other three groups (and the one of particular interest is that between the endogenous and reactive groups) are not significant.

It might be considered that to make such a classification *solely* on aetiological grounds is unsatisfactory, since this could be done better if the symptoms were used as well. It is generally considered that endogenous depression tends to be of the retarded type, and reactive depression of the anxious-agitated type. It is also considered that the former responds better to E.C.T. than the latter, but since this is the point of the investigation, it was thought better to avoid difficulties, and to adhere solely to an outside criterion. On an entirely different basis, the syndromes of depression were investigated, and this has been reported elsewhere (Hamilton and White, 7), together with clinical details and case histories.

Among the 49 patients were 6 who did not respond at all to E.C.T., and 5 of these were in the D.E. group. They were severely depressed, retarded and felt guilty to the point of delusions. Two of the six had made grimly

TABLE II
Outcome in Clinical Groups

		Endo- genous	Doubtful Endo- genous	Doubtful Reactive	Reactive	Total
		E	DE	DR	R	
Number of cases	..	11	9	11	18	49
Total initial score	..	580	431	489	723	2,223
Sum of squares	..	—	—	—	—	106,607
MEAN INITIAL SCORE	..	52.7	47.9	44.5	40.2	45.4
F=3.74 P<.05						
Total final score	..	144	303	141	341	929
Sum of squares	..	—	—	—	—	29,557
MEAN FINAL SCORE	..	13.1	33.7	12.8	19.9	19.0
F=4.47 P<.01						

determined attempts to kill themselves. The patients in the D.E. group had good well-adjusted personalities before they fell ill, and only the presence of minor psychological stresses prevented them from being regarded as purely endogenous. Clinically, there was no difference in the symptoms between the D.E. group, who did badly, and the E group who responded quite well to treatment.

3. Ratings

The patients had a mean initial score on the rating scale of 45.4 points, ± 11.0 S.D. (range 21 to 66). Their mean final score was 19.0 ± 15.8 S.D. (range 0 to 67), which indicates considerable improvement in the group as a whole. Although the patients were originally selected on the (clinical) grounds that they needed and would benefit from E.C.T., some of them showed no improvement at all. Only 5 patients were completely freed from all symptoms, receiving a zero score.

TABLE III
Distribution for Rating Scores and Age

Range					Number of Patients		Age
					Initial Score	Final Score	
0-9	..	..	..	..	0	15	0
10-19	..	..	..	..	0	13	0
20-29	..	..	..	..	3	12	4
30-39	..	..	..	..	11	3	4
40-49	..	..	..	..	18	3	9
50-59	..	..	..	..	9	2	16
60-69	..	..	..	..	8	1	16

The relation between the initial score and final score can be expressed as a correlation of .28, which is statistically significant, i.e. significantly different from zero, at the 5 per cent. level. This does not adequately represent the relation between the two. Table IV shows that there is a considerable increase in the final score as the initial score increases, except for the group with the lowest initial score. With this exception, the results show that the more ill the patient, the more likely is the outcome to be worse.

TABLE IV
Relation Between Initial and Final Scores

Initial score	..	20-29	30-39	40-49	50-59	60-69	Total
Number of cases		3	11	18	9	8	49
Total final score		60	129	265	258	217	929
MEAN FINAL SCORE		20.0	11.7	14.7	28.7	27.1	19.0
Sum of squares	..	—	—	—	—	—	29,557

$F=2.60 \quad P=.05$

Such a relationship, where the graph is V or U-shaped, is described as non-linear. In this case, it suggests the hypothesis that these few patients with low scores are of a different type from the others.

It was mentioned above that some symptoms were excluded from the total score on the rating scale. The first, Diurnal Variation of symptoms, is not a measure of intensity of illness but a classification of the other symptoms. It was absent in 24 of the 49 patients, who had a mean final score of 20.1 points, whereas the 25 who showed this feature had a mean final score of 17.9 points. The difference is not significant statistically. Depersonalization of some degree was present in only 7 patients, who had a mean final score of 28.9, whereas those who did not have the symptom had a mean of 17.3 points. The difference is not quite large enough to be significant ($F=3.37, P<.10$). Obsessional symptoms, interpreted strictly, were found (mildly) in only one patient.

Paranoid symptoms were found in 11 patients. It can be seen in Table V that mean final score increases steadily with this symptom. The statistical test shows that this trend is significant. This is in accord with clinical experience, e.g. Chodoff *et al.* (1).

TABLE V
Paranoid Symptoms and Final Score

Symptom score	..	..	0	1	2	3	4	Total
No. of patients	..	..	38	5	4	1	1	49
Total final score	..	..	620	126	126	12	45	929
MEAN FINAL SCORE	..	..	16.3	25.0	30.5			19.0
Sum of squares	..	..	..	..	..	29,557		
Sum of cross-products	..	..	..	..	..	594		

Analysis of Variance

Source	d.f.	SS	MS	F	P
Between groups:					
Regression	1	1,219.61	1,219.61	5.30	<.05
Residual	3	596.30			
Within groups	44	10,128.01	230.18		
Total	48	11,943.92			

When a number of items in a rating scale are summed, the resulting total may be regarded as an "index number" which gives some sort of impression of the way the item scores run. Obviously a good deal of information is lost in this way. More information can be retained by using more index numbers (Hamilton, 3). When these are calculated, by suitable weighting of the individual

items, so that they are uncorrelated in the sample group, the numbers are known as orthogonal factor scores. Such factors can be of great intrinsic interest. Four of them have been calculated, and it would appear that the first is a measure of retarded depression, and the fourth measures a syndrome of depression found in abnormal personalities (Hamilton and White, 7). The correlation of these factors with outcome, from the first to the fourth respectively, is $\cdot 23$, $\cdot 17$, $\cdot 27$ and $-\cdot 09$. Since the third is the only one that reaches statistical significance, it is therefore of considerable interest. This is confirmed when the correlation with outcome is calculated separately for the four clinical groups described above. The correlations are: for group E $\cdot 43$, group D.E. zero, group D.R. $-\cdot 20$ and group R $\cdot 07$. Thus the correlation between the third factor and outcome is largely confined to the patients with endogenous depression. Of course, the numbers are too small for any conclusions to be drawn from these results.

4. *Funkenstein (Mecholyl) Test and Age*

In the abbreviated form, this test is done as follows: the patient is kept lying down and his blood pressure taken regularly until it settles down to a steady level. The patient is then given an intramuscular injection containing 10 mg. of methacholine, and the blood pressure recorded regularly for a maximum of 25 minutes, or less if it reaches a steady state sooner. It has been claimed that the individual variations in response are related to prognosis, and there is now a considerable literature on the subject. This has been reviewed by Feinberg (2), whose general conclusions are that the empirical value of the test has not been established, and that its theoretical basis is still insecure.

In this inquiry, the mecholyl test results have been used in the form proposed by Hamilton (4). This gives two items of information (which are independent and of good reliability) from the test: the basal blood pressure, and the "drop" in blood pressure, obtained by calculating the slope of the ascending portion of the curve and determining from it the blood pressure at 2 minutes after the injection.

The basal blood pressure has a correlation of $-\cdot 11$ with outcome, and this is not significant statistically. The "drop" in blood pressure has a correlation of $\cdot 26$, and this is barely significant. Closer examination of the results shows that there is a non-linear relationship here, the graph forming a shallow U-shaped curve. Thus, the overall result is disappointing, but the data suggest that the test merits further investigation. It is not relevant to discuss here the relation between the test results and the age of the patients, as they are of primary interest in relation to the test (Hamilton, 6). It is sufficient to mention that the correlation between age and outcome is the negligible one of $\cdot 14$, contrary to accepted belief.

5. *Body-Index and Weight*

Among other physiological and constitutional factors considered are the Rees-Eysenck Body Index and the Weight. The former is the ratio between height and width of chest, multiplied by 100/6 to give a mean of 100. An index below this corresponds to a pyknic build, and above to a leptosomatic build. The mean for the patients is $103\cdot 6 \pm 7\cdot 9$ S.D. The correlation with outcome is $\cdot 29$, which is statistically significant (see Table VI). Detailed examination of the means of final scores shows that the relationship is non-linear, the graph

being shaped like an inverted V. The impression given is that the extreme body types do better than the average. This must not be regarded as more than a suggestion to be considered; the statistical test shows only that pyknic patients tend to do better. This is in agreement with clinical experience.

TABLE VI
Relation Between Body Index and Final Score

Body Index	Below 96	96-100	101-105	106-110	Over 110	Total
Number of cases ..	6	9	16	10	8	49
Total final score ..	49	109	357	284	130	929
MEAN FINAL SCORE ..	8.2	12.1	22.3	28.4	16.2	19.0
Total score (BI) ..				5,078		
Sum of squares (BI) ..				529,260		
Sum of cross products ..				98,024		

Analysis of Variance

Source	d.f.	SS	MS	F	P
Between groups:					
Regression	1	1,015.45	1,015.45	4.61	< .05
Residual	3	1,235.41			
Within groups ..	44	9,693.06	220.30		
Total	48	11,943.92			

The correlation between weight and outcome is $-.31$, the second highest correlation obtained in this investigation. The negative coefficient indicates that the greater weight is associated with a better outcome. The weights were measured on admission to hospital and are therefore not the normal weights of the patients. As the mean weight is $66.6 \text{ kilos} \pm 10.4 \text{ S.D.}$ (range 49.0 to 98.9 kilos) and the loss of weight in a patient is rarely as large as 10 kilos, the substitution of the normal weight for the current weight is not likely to make much difference to the results.

These two variables are closely related, of course, but it should not be thought that they are giving the same information. The correlation between them is $-.44$.

6. Length of Illness

The correlation between length of illness and outcome is $.46$, the highest correlation found in this investigation (see Table VII). This does not adequately represent the relationship between the two, which is non-linear. It can be seen from the table that except for the shortest histories, the mean outcome is progressively worse with increasing length of illness. (The reason for the odd assortment of history lengths at the top of the columns is that there was only one case each for lengths of 1, 5, 7 and 10 months.) It would be mistaken to conclude from the data that the best time to administer E.C.T. is at the third to fourth month of the illness. What the data signify is that those patients who presented themselves for treatment at the third and fourth month of their illness, were the ones who responded to it best.

7. Background Data

By means of statistical tests, the relations between various background variables and outcome were investigated. The results can be summarized briefly. It makes no difference to the outcome whether the patients do or do

TABLE VII
Relation Between Length of Illness and Final Score

Length of illness (months)	1-2	3	4	5-6	7-9	Over 9	Total
No. of patients ..	7	9	6	10	7	10	49
Total final score ..	196	83	63	163	152	272	929
MEAN FINAL SCORE ..	28.0	9.2	10.5	16.3	21.7	27.2	19.0
Total score for length of illness ..					356		
Sum of squares for length of illness ..					4,102		
Sum of cross-products ..					8,063		

Analysis of Variance

Source	d.f.	SS	MS	F	P
Between groups:					
Regression ..	1	1,138.44	1,138.44	5.27	< .05
Residual ..	4	1,519.29			
Within groups ..	43	9,286.19	215.96		
Total ..	48	11,943.92			

In this table, to avoid the distorting effect of a few very long histories, all histories over 1 year have been taken as 18 months. This reduces the correlation to .31.

not have a history of mental illness in the family, neurotic traits in childhood or adult life, psychological or physical precipitation of illness, whether the onset of illness is sudden or gradual, the course steady or fluctuating; and finally, the number of previous attacks of illness also make no difference.

8. *Hobson Score*

An interesting investigation of prognostic variables was made by Hobson (8). He found that a favourable outcome was related to the presence of an obsessional personality, sudden onset, self-reproach in the symptoms and the retention of insight. Associated with an unfavourable outcome were: neurotic traits in childhood and in adult life, a fluctuating course, duration of illness over a year, the symptoms of hypochondriasis, pronounced retardation and depersonalization, emotional lability, hysterical attitude to illness, hysterical and ill-adjusted previous personality. By counting one point for the presence of an unfavourable factor and for the absence of a favourable one, he obtained a total score which was inversely related to outcome, i.e. the higher the score, the worse the outcome.

These items were recorded and where the data were suitable, statistical tests were done on them, as above. Although individual items may not show significant results, if they all run the same way, the total may do so. Hobson scores were calculated for the patients and their correlation with outcome is .18, which is not significant.

It is unfortunate that Hobson has not followed up his work, but Roberts (9) repeating it on female patients, most of whom were admitted to the psychiatric beds of a general hospital, was able to confirm his findings, with the remarkably high correlations between Hobson's score and outcome of .73, interviewing after 1 month, and .67 at the end of 3 months.

In his paper, Hobson emphasized that certain items were difficult to assess. These included details of the history of the present illness, previous illnesses, personality and the family history. We would agree with this and extend the area of difficulty much wider. It was usually possible to obtain a fairly clear background history from patients who were reasonably young and not too ill. In the older patients details of their early life, such as the presence of

neurotic traits in childhood, were almost impossible to obtain. Details of the present illness had often to be obtained from a relative, not always a satisfactory procedure. It would appear that our patients were much more severely ill than Hobson's, who were mainly voluntary admissions to the Maudsley Hospital, and Roberts's, and this may account for the difference between our results and theirs.

Hobson's emphasis on the deleterious effects of an unstable background and neurotic personality are not in accordance with our experience, as the majority of cases of this type did well.

DISCUSSION

There are many difficulties in the interpretation of these results. The most important are those introduced by the fundamental clinical problems of relapses and fluctuations. After treatment, a patient may show improvement, but his condition is labile and his assessment may change considerably from his best to his worst. An average can always be taken, of course, but this is not necessarily very informative. The situation is even worse when the patient responds easily to treatment, but just as easily relapses. Sometimes a second or third course of treatment may lead to an enduring response, but this raises the question of determining the optimum course of treatment. The nature of the response to treatment may also cause difficulties. A patient's depressive symptoms may diminish or disappear, leaving those of anxiety and tension; indeed, the latter may even increase when the blanketing effect of the former is removed. Such a partial response is inadequately represented by an overall assessment, even when it is made more exact by ratings. To deal with these problems, it would be necessary to particularize improvement, with respect to specific symptoms and to changes with time. Unless this is done, partial responses and fluctuations appear as errors which obscure the results obtained.

Generalizing from these results must be done with caution. Clinical judgment is good on the whole and the careful selection of patients leaves little room for the variables studied to show their effect. The patients in this group were men who were all very ill, and it would be unwise to assume that these results would hold for mildly ill patients or for women.

Selection is not the only reason for the small size of the correlations with outcome. A correlation measures a general trend and is diminished by a non-linear relationship. For example, patients with a very short or very long history tend to do worse than those in between, and those with a very small or very large body-index tend to do better. If these findings are confirmed, then it would be possible to increase the correlations by taking into account the deviation from the mean, as well as the general trend.

There is no need to stress the practical value of accurate prognoses. The usual method of doing this is by classification: retarded patients respond better than others, and this patient is retarded, therefore he is likely to do well; young patients do worse than older ones, and he is young, therefore he is not likely to do well and so on. When the clinician makes an individual *prediction*, he combines the categories mentally, giving due weight to the different ones. This process is based upon skill derived from clinical experience.

In this investigation, the predictive variables have been quantified, and this opens up the possibility of a suitable quantification of the process of weighting. Among the highest correlations with outcome are Length of Illness .46, Weight — .31, Body Index .29, Total Initial Score .28, Score on

Factor Three .27, and Funkenstein test "Drop" .26. Leaving out the Factor Score, which is laborious to calculate and is derived from the ratings, already included in the Initial Score, we are left with five items, all of which can be obtained without difficulty, even from the uninformative patient. They cannot be summed as such because they are not independent, i.e. they are correlated, but the technique of multiple correlation takes this into account, and gives each variable a weight related to its contribution to the prediction, over and above that of all the others. The result is the maximum possible correlation possible from a weighted sum. In this case, the multiple correlation reaches .62, a result which is about as high as that generally found in the field of personality study, and may even be regarded as surprisingly high.

TABLE VIII
Correlation and Regression Weights

	History	Weight	Body Index	Initial Rating	Mecholyl "Drop"	Final Score	Regression Weights
History	1.000	-.024	-.002	.148	-.044	.459	.448
Weight	-.024	1.000	-.330	-.385	-.256	-.305	-.138
Body index ..	-.002	-.330	1.000	-.031	.162	.292	.223
Initial rating ..	.148	-.385	-.031	1.000	.399	.283	.103
Mecholyl "drop" ..	-.044	-.256	.162	.399	1.000	.262	.169

Multiple R = .622

Nevertheless, optimism cannot but be restrained. In the first place cross-validation on another group of patients will show a smaller correlation. The weights which give a correlation of .62 in this group, will not be the best for another group, owing to fluctuations of sampling, and therefore this correlation is the maximum which one can hope to achieve. Secondly, the actual reduction in error of guessing, resulting from such a correlation, is small. This can be illustrated as follows: given no information about a patient other than that he is of the type studied, what can we say of his response to treatment? The best guess we can make, the one which will give the minimum error in the long run, is that he will have an average result. It is an improvement to give the guess in the form of a range of scores, say, two standard deviations below and above the mean. This covers about 95 per cent. of the population, and is equivalent to saying that the patient is likely to score somewhere a little above the minimum and a little below the maximum scores. We shall then be correct about 95 per cent. of the time. Obviously, this is merely a roundabout way of saying that we do not know what the result will be. When we are given the data on the five variables for the patient, we can use the regression equation to calculate his expected final score, and because of the multiple correlation we can narrow down the range of scores to 1.6 standard deviations above and below the predicted figure, with the same 95 per cent. accuracy. Obviously, except for extreme scores, this is no great practical improvement, but these results are only a first step, and they do point the way to further developments.

SUMMARY

A group of 49 male patients suffering from severe depressions, have been investigated to determine the factors related to outcome after treatment by E.C.T. By means of a rating scale for assessing the clinical condition,

the relationships can be expressed in the form of correlation coefficients. The highest correlations are Length of Illness $\cdot 46$, Paranoid Symptoms $\cdot 32$, Weight $-\cdot 31$, Body-Index $\cdot 29$, Initial Score on the rating scale $\cdot 28$. These are all statistically significant, although it has been shown that the correlations under-estimate the relationship. Other correlations of interest (but not significant) are the "Drop" in blood pressure in the Mecholyl test $\cdot 26$, and the Hobson score $\cdot 18$. A number of other variables were found to have non-significant relationships. They include a family history of mental illness, neurotic traits in childhood, or adult life, psychological or physical precipitation of illness, sudden or gradual onset, fluctuating course, previous attacks, depersonalization, diurnal variation, age and blood pressure.

Five variables give a multiple correlation of $\cdot 62$. The significance of these results and the problems of their interpretation are discussed.

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A REVIEW OF THE LITERATURE ON THE RELATIONSHIP OF EPILEPSY AND INTELLIGENCE IN SCHOOLCHILDREN

By

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A. INTRODUCTORY

A REVIEW such as this is not the place, nor has it the space in which to discuss the nature of intelligence. Some conclusion, however, must be reached as to the factors to be considered in estimating any correlation, positive or negative, between level of intelligence and degree of epilepsy.

Although modern writers on mental deficiency still quote I.Q. figures as indicative of the degree of defect (see Table I), enlightened opinion now tends

TABLE I
Definition of Mental Category by I.Q. Rating

Authority	Date	Dull	Feeble-minded	Imbecile	Idiot
Stern, W.	1914		80-71.	70-61	
Terman, L. M., p. 79	1916	90-80	70-	50-	25/20-
Burt, C., pp. 168, 188	1921		70- (ch) 50- (ad)		
Lewis, E. O.	1929		70- (ch) 65- (adol) 60- (ad)	50/45- (ch) 45/40- (ad)	20-§
Pintner, R.	1933		60- (defective)		
Burt, C.	1937		70- (supervisory) 50- (institutional)		
Bernreuter, R. G. and Carr, E. J.	1938		60- (defective)		
Kuhlmann, F.	1939	94-85	75- (defective) 84-75 (borderline)		
Porteus, S. D.	1941		65/60 (defective)		
Wechsler, D., p. 36 ff.	1944	90-80	65- (defective) 79-66 (borderline)		
Penrose, L. S.	1949		69-50	49-20	19-
Wallin, J., p. 22†	1949	94-59	70-48	65-21	17-
Kirk, S. A. and Johnson, G. O.	1954		70-50	50/40-25/20	25/20-
Mayer-Gross <i>et al.</i> , p. 54	1954		†70-	†50-	†20-
Henderson and Gillespie, p. 585*	1956	90-	70-	40-	20-
Lovell, K.	1958	85-	70-	55-	25-

N.B.: ch—children; adol—adolescents; ad—adults.

* All figures approximately.

† “Some authorities would say this is too high and some too low.”

‡ In an account of a survey carried out in 1911.

§ “Few idiots are found with an I.Q. as high as 20.”

to relegate them to the field of broad medical statistics, and is convinced that as a sole criterion of intelligence the I.Q. is not a valid measure (Bridge, 1934; Clarke and Clarke, 1958, p. 50, 53; Hilliard and Kirman, 1957, pp. 159 ff.). Clarke points out that the I.Q. lacks correlation with social behaviour (Wallin, 1949; Wechsler, 1944), is unreliable (Shapiro, 1951; Tizard, 1953), is inconstant* and may vary with the particular test used. Brody and Williams, 1950, use even more forceful terms in suggesting that "the I.Q., at best a crude and misleading measure, is no longer a subject of much interest".

Jones, 1953, gives a good critical summary of all types of psychological tests given to epileptics, adults as well as children, and comments that "there are few valid results in the literature, due probably to the inadequacy of research techniques". The tendency is, however, as intelligence tests and environmental factors are handled in a more sophisticated fashion, to find that the incidence of so-called deficiency in epilepsy, as in delinquency, decreases (Williams, 1958).

B. STATISTICS AND OBSERVATIONS ON I.Q.s OF EPILEPTIC CHILDREN

Whatever may be the final statistical outcome of any investigations into the educability of epileptics and the relationship of intelligence to epilepsy, the broad fact remains, from history since the earliest times (Temkin, 1945) and from common personal experience, that "Epilepsy is compatible with all levels of intelligence from genius† to idiocy" (Wallin, 1949, p. 367).

From such studies as have been made and their findings published, we get a very indefinite picture of the level of intelligence of epileptics. There have been one or two generalized observations which purport to find no difference between the I.Q.s of epileptics and of the rest of the population (Sheps, 1947; Metrakos *et al.*, 1954; Wallin, 1949, p. 384; Harrower-Erickson, 1941, p. 568; Lennox, 1946, p. 58; Waggoner and Sheps, 1944; Folsom, 1953; de Haas, 1958, p. 48) but to take this statement literally is to oversimplify the situation. Most of the work has perhaps naturally been done on schoolchildren or on institutionalized children and adults. No objectively conclusive results seem to be available, nor is there quantitatively a great measure of agreement. As the W.H.O. technical report No. 130, p. 17, says: "The main problem has been to get a truly unbiased sample for testing."

In general, institutional epileptics have given a mean I.Q. lower than normal (Davies-Eysenck, 1952; Collins, 1941; W.H.O., 1957, p. 18; Harrower-Erickson, 1941, p. 549; Donovan, 1952). Since, however, subnormal epileptics may be institutionalized for specific reasons other than epilepsy, there would appear to be among the institutional epileptic population, certain individuals who show either a retardation in mental development or a deterioration from a standard once achieved, and who by this shortcoming lower the statistical average for the group as a whole. It will be seen that group tests or grouped analyses of

* Also vide Gray (1936) and Schmidt (1946).

† In substantiation of the statement that "some of the world's great and near-great have reputedly suffered from some kind of convulsive seizures", Wallin (1949, p. 367) quotes the cases of "... Lord Byron (mild seizures); Swinburne (jerkings when excited, temper-tantrums, periods of dipsomania, falling during attacks); Edward Lear (seizures almost daily ...); Blaize Pascall ...; Gustave Flaubert (swoonings, fallings and nocturnal convulsions); Guy de Maupassant ...; Julius Caesar (headaches and seizures); Alexander the Great; Peter the Great (lifelong short and mild attacks); Alfred the Great; William III of England; Louis XIII of France; Charles V of Spain; Caligula ... " and others. Amongst religious leaders it is also claimed that Moses, St. Paul and Mohammed were subject to attacks which we should today most probably diagnose as epileptiform, and we may add the well-known examples of King Saul, Dostoevsky and Van Gogh.

individual tests will fail to throw much light on this problem. Rather should consideration be given to the specific conditions found in individual cases. Attention is given later in this review to attempts in the literature to evaluate these possibly causative conditions.

Very little work seems to have been done on the I.Q.s of extramural epileptics, but it has been suggested that many of them have average or above-average intelligence (Harrower-Erickson, 1941, p. 568; Wallin, 1949, p. 384; Putnam, 1945, p. 32) even to the extent of being able profitably to sit for a degree (Cohen, 1958).

It would seem that the greatest factor in determining the variations has been the selection of material or the environmental conditions of the test. Halstead (1957) finds that "the (verbal) intelligence is related to the kind of school attended and to the type of epilepsy, with higher I.Q. in normal schools, in idiopathic epilepsy and in *petit mal*".

C. OTHER STATISTICS ON THE ASSOCIATION OF EPILEPSY AND MENTAL DEFICIENCY

From time to time claims have been made to have found significant associations of epilepsy with mental deficiency, or to have found significantly large proportions of convulsive disorders in mentally defective populations.

Penrose (1949, p. 199) found that 27.6 per cent. of 1,280 patients in a mental hospital (Colchester Survey) were epileptic. Yannet (1945, p. 83 ff) reported convulsions in institutionalized mental defectives in:

- 6.6 per cent. of familial cases
- 18.4 per cent. of undifferentiated inmates
- 32.2 per cent. of the cerebral palsied
- 35.7 per cent. of traumatic cases
- 41.2 per cent. of infection cases

or, grouping by mental grades, in:

- 21 per cent. of idiots
- 16 per cent. of imbeciles
- 9 per cent. of morons

These figures may be compared with Tredgold's (1937, p. 241 ff), which are based on an earlier investigation of epilepsy "of simple variety" (probably idiopathic)—largely institutional cases in which convulsions were found in:

- 70 per cent. of patients presenting signs of gross lesions
- 37 per cent. of primary oligophrenics (idiopathic without lesions)

and in:

- 56 per cent. of idiots
- 42 per cent. of imbeciles
- 11 per cent. of morons

Wallin (1949, p. 368) comments that the improvement shown in Yannet's figures over Tredgold's may probably be explained by the discovery of more effective treatment during the intervening years, and attributes figures of his own (1917, p. 363) to the effect that following a psycho-clinical survey of "an entire colony for epileptics (the New Jersey State Village for Epileptics) . . . about 85 per cent. of the inmates were feeble-minded from the standpoint of intelligence (including cases of both oligophrenia and dementia), the great majority (61.5 per cent.) classifying as high-grade cases (morons)".

TABLE II

Statistics of I.Q. Tests Given to Epileptic Subjects

Investigator(s)	Date	Cases	Place	I.Q. All	Type	Mean I.Q.	Range
Tylor-Fox	1924	150c	Lingfield, U.K.	66	Girls	65	
Halstead	1947		Chalfont, U.K.		All	66	
Hillkevitch	1946		Dixon, U.S.A.		Petit mal	66	
Tylor-Fox	1924	150c	Lingfield, U.K.		Boys	71	
Fetterman and Barnes	1934	150ca		74	All	74	{ 40% < 70 34-133 30-129 36½% feeble-minded
Hillkevitch	1946	66	Dixon, U.S.A.		Grand mal	75	
Lennox and Collins	1945				Brain lesion	77	
Halstead	1947		Lingfield, U.K.	80	All	80	
Dawson and Conn ..	1929	49c	Glasgow, U.K.	80	All	80	{ 49-117 22.4% feeble-minded 70-90
Baker	1944		Detroit, U.S.A.	80	All	80	
Tenny	1955		Detroit, U.S.A.	84	All	84	
Sullivan and Gahagan	1935	103c	Los Angeles	88	All	88	
Somerfield-Ziskind and Ziskind	1940		Los Angeles		Symptomatic	88	{ 19.3% feeble-minded 11-141
Zimmermann <i>et al.</i> ..	1951				Symptomatic	89	
Zimmermann <i>et al.</i> ..	1951				Traumatic	89	
Zimmermann <i>et al.</i> ..	1951				Grand mal	91.2	
Zimmermann <i>et al.</i> ..	1951				Grand mal and idiopathic	91.5	
Somerfield-Ziskind and Ziskind	1940	100ca	Los Angeles	93	All	93	{ 19.3% feeble-minded 11-141
Zimmermann <i>et al.</i> ..	1951	100c		93.5	All	93.5	
Lennox and Collins	1945				No lesions	96	
Henderson	1954	365c	U.K. normal schools		Normal	95.5	
Collins and Lennox ..	1947				Brain lesions	96.7	
Collins and Lennox ..	1947	11c			Grand mal and psychomatic	102.2	
Collins and Lennox ..	1947	25c			Grand mal and petit mal	102.7	
Collins and Lennox ..	1947	100c	Los Angeles	104.1	All	104.1	
Collins and Lennox ..	1947	36c			Grand mal	105	
Sullivan and Gahagan	1935				Non-epileptic	105	
Zimmermann <i>et al.</i> ..	1951				Idiopathic	105.5	
Lennox and Collins ..	1945				petit mal	108	
Collins and Lennox ..	1947	8c			Non-epileptic	108	
Collins and Lennox ..	1947	18c			Psychomatic	108.6	
Collins and Lennox ..	1947				Petit mal	113	

(a) Range of mean I.Q.s given as 70-90; (b) basis of 186 co-twins by Form L on Stanford-Binet or Wechsler-Bellevue; (c) children; (ca) children and adults; (d) observed over 3 years; (e) mostly idiopathic cases; (g) out-patients.

TABLE IIA

Statistics of I.Q. Tests Given to Epileptic Subjects

Investigator(s)	Date	Cases	Place	N.B.
Wallin	1911	333	New Jersey, U.S.A. { Epileptic Village {	Binet age 3 3-7 8-12 13+ Percentage 4 22 65 6
			66 per cent. feeble-minded	
Wallin	1913		Ditto with more conservative standard of test: 55 per cent. feeble-minded	
Wallin	1911		St. Louis Psycho-Educational Clinic: 65 per cent. feeble-minded	

(Cases referred mainly on account of mental limitations)

Donovan .. 1952 .. Lingfield, U.K.: 40 per cent. estimated I.Q. < 85

(f) Adult cases over 24 years of age.

Working "the other way round", Lennox (1946, p. 51), examined the records of 1,640 clinic and private (non-institutional) idiopathic epileptics and found that:

- 67 per cent. were mentally normal.
- 23 per cent. were slightly subnormal.
- 9 per cent. were "definitely deteriorated".
- 1 per cent. were "markedly deteriorated".

These percentages are apparently based on estimated rather than on tested intelligence.

A paper worth noting in spite of criticism (Mayer-Gross *et al.*, 1954, p. 62; Slater, 1936) is by Duncan, Penrose and Turnbull (1936), who made a " cursory assessment of the intelligence of the standing population of a large mental hospital and of the newly-admitted patients . . . Of the new admissions:

- 24 per cent. of schizophrenics.
- 27 per cent. of manic-depressives.
- 60 per cent. of epileptics.
- 22 per cent. of sufferers from organic psychoses

were mentally defective, and the proportions in the standing population were considerably higher".

D. DETERIORATION OF INTELLECTUAL STATE OF EPILEPTIC CHILDREN

It is important to stress the necessity to distinguish intrinsic from accidental retardation—possible the result of emotional disorder, poor teaching or lack of stimulation in the case of institutionalized children (Henderson and Gillespie, 1956, p. 667). It may even be worth taking into account the fact that "mental laziness is a form of defence reaction" (Loewy, 1951, p. 50, 43) in that the child finds retreat into a world of phantasy less demanding than reality.

Two surveys of the comparative intelligence of epileptic and normal children may be referred to as typical.

Wallin (1917, p. 369), in one of the earliest surveys undertaken in this field, finds that "epileptic children never came to within 50 per cent. of the scores of normal children in tests of mental capacity". He found their scores always inferior to those of normal controls, their efficiency relative to the latter being anything from 80 per cent. in the best comparison of test for test to only 15 per cent. in the most divergent. It is worth quoting his opinion that this was partly dependent upon "the retarded rate of ideational activity which seems to characterize the average epileptic". Four years later in a re-check, Wallin (1917, p. 381) found an average gain of only about 6 months educational progress. He found that 16 out of 22 retested patients had retrogressed, 2 had gained ground and 4 had maintained an approximately similar position.

Halstead (1957), comments that an analysis of experimental test results "shows that the epileptic children are especially handicapped in comparison with the control group by *slowness in thinking* (which may be partly due to the effects of the drugs), *immediate memory* and *manual dexterity*". He finds much less discrepancy between his epileptic children and his normal controls than did Wallin in 1911, but it is difficult to say how much this was due to the nature of the tests or more especially to the technique of testing. He gives the composite score deviation of the epileptic children in his sample as approximately minus 9 months of mental age compared with the control group. A tendency to

increased scatter in scores on intelligence testing is found also by other workers.

Contradictory reports that epileptics compare *more* favourably (Halstead, 1957) and *less* favourably (Bradley, 1946) with normal controls in *mathematical* tests indicate the need for still further enquiry, but imbalance of attainment in such diverse activities as verbal tests of intelligence, numerical calculations, etc., in the individual, such as appear in these surveys, need not strike one as strange in the light of experimental evidence quoted by Wilkie (1953, p. 108), "It is possible for local injury to the brain to disorder one faculty, factor, power or what-you-will of the mind more gravely than the others. This fact has been established beyond all reasonable doubt (Weisenburg and McBride, 1935) . . .".

Reasons for the failure of epileptic children in intelligence tests and especially in retests have been given as "lack of concentration and inadequacy in recent memory" (Tylor-Fox, 1924), "typical slowness of mental reaction and marked failures of memory and motor promptitude" (Burt, 1937), and "vacillation in ability to recall material which has been previously learnt" (Bradley, 1947). Ninde (1927), found in 2,000 institutionalized epileptic children that their memory span for digit repetition was only half as good as that of normal children, and Earl (1936), found them "lacking in drive" and "in constant need of stimulation", which is certainly borne out by experience in special schools for epileptic children today.

Apart from the work quoted above—mainly of an educational or at least a pedagogic nature—it is difficult to make out a case that the *average* epileptic can be mentally differentiated from the *average* normal person. It is nevertheless commonly found that individual epileptics often do present symptoms at one and the same time both of epilepsy in some form or other and of mental deficiency or deterioration over a period of time. (Reference here is not intended to the syndrome Epiloia.) It may be well to study work which has been done with patients of this kind, firstly to discover whether in fact the two conditions are significantly frequently found in association and secondly whether this association is merely concomitance or whether there are any indications of either a common causal factor or direct suggestions that epilepsy *per se* can account for the mental shortcoming.

Tredgold (1937, p. 275), in defining a group of "true epileptic amentia", includes only about 1 per cent. of oligophrenics of all ages, but he gives a depressing prognosis: ". . . the persistence of fits gradually strips these people of any acquirements they may have possessed, and in the majority of cases dementia is but a question of time." He has not seen a single case in which this deficiency, once produced, had been cured. Hall (1947, p. 152), distinguishes epileptic dementia as "progressive mental deterioration as distinct from intellectual deficiency" and says that it "may be revealed by slowing of mental activity, limitation of interest, impairment of immediate memory and a functional aphasia as a result of which difficulty is experienced in recalling a particular word . . ." The similarity of these symptoms with those found by Halstead and other workers (*cit. supra*) is marked. Mayer-Gross *et al.* (1954, p. 385), confirm it as a stage in which "there is not only an incapacity to deal with what is new, but also a gradual loss of the old and well-established pattern . . . at last a state of incoherence is reached which may well resemble a schizophrenic end-state".

Henderson and Gillespie (1956, p. 560), describe this condition of "epileptic dementia" very well: "This is a state of very gradual mental decline and enfeeblement found most often in those cases where the epilepsy has begun in

childhood or at an early age, and has been severe, leading to institutional treatment. The affected individual becomes more self-centred as he loses interest in his environment . . . his mental content becomes very limited and his memory poor . . . there develops sooner or later in many cases a functional aphasia . . . In contradistinction . . . reading, writing and spelling may be surprisingly well done. Composition is rambling and pedantic. Speech and thinking become slower and perseveration is sometimes present in excessive degree. Speech may lose its normal inflections—the so-called ‘plateau speech’ resulting . . . The patient becomes more and more susceptible to flattery . . . indulges more and more in boasting . . . vanity increases and yet care of personal appearance decreases; he becomes less amenable to discipline . . . increasingly inactive and lazy . . .”

The presence of such individuals in institutions—and the above paragraph gives a vivid pen-picture of some children in special schools for epileptics—naturally prompts the question as to whether such deterioration is actually produced by the epileptic attacks and whether the often severe convulsions may not have considerable effect on the mentality of the individual. Wallin (1949, p. 383), flatly denies that “epilepsy produces more feeble-mindedness or insanity than do some other diseases of the brain—for instance encephalitis or meningitis”. The question is discussed, however, in greater detail in subsequent sections of this Review.

TABLE III

Statistics and Observations on Deterioration of I.Q. on Testing After a Period of Time

Investigator(s)	Date	I.Q. on Retest			N.B.
		Increase	Same	Decrease	
		Deterioration	Alleged		
Tylor-Fox . .	.. 1924 1950	37%	41%	22%	High incidence major fits a factor in deterioration; 8 per cent. seriously deteriorated. Found “a progressive narrowing of mental horizon”.
Dawson and Conn	1929			Decrease	General tendency to decrease. Average drop in I.Q. 88 to 66. Some deterioration very serious.
Adie . .	.. 1924			Decrease	Marked deterioration characteristic of epilepsy but not of pyknolepsy.
Hillkevitch . .	1946	66%		33%	Mean I.Q. dropped 4.2 points. Range I.Q. change —44 to +24.
W.H.O. Report (p. 13)	.. 1957			Decrease	Deterioration result of status and probably also of many frequent severe grand mal seizures.
Herd (p. 101)	.. 1930			Decrease	Epileptic dementals tend to have diminishing I.Q. Petit mal patients almost as liable to deterioration as grand mal.
Wallin (p. 368)	.. 1949				Dementia produced by severe, frequent, long continued grand mal.
Henderson and Gillespie (p. 560)	1956				Extreme deterioration a definite syndrome.
		Uncertain or Qualified			
Hall (p. 152)	.. 1947		?		Only in extreme cases.
Hilliard and Kirman (p. 32)	1957		?		General and mental state of most epileptics does not deteriorate, but fits may harm the brain and affect intelligence. Difficult to know how much due to fits and how much to underlying causes.

Mayman and Rappaport	1947	?			As yet no certain answer. Deterioration occurs but not characteristic.
Hodskins and Yakolev	1931	?			When deterioration occurs it is associated with cerebral palsy.
Collis (p. 32) (quoting Phelps)	1947	?			Deterioration found when epilepsy associated with cerebral palsy.
Lennox	1946		9%		(1 per cent. seriously) but 29 per cent. over long periods (25 years).
Paskind	1932		6%		Over a period of 6 years.
			15%		Over a period of 25 years.
					Mostly no deterioration (evidence obtained by questionnaire, not tests).
Kirman	1956	?			Tendency for cases of cerebral palsy with epilepsy to be less intelligent.
Pintner <i>et al.</i>	1941	?			Indicate that only a small number of epileptics have marked deterioration, with greater tendencies to lowering of the I.Q. among the more severe cases of long duration.
No Deterioration Found					
Fetterman and Barnes	1934		33%	9%	50%
Somerfield-Ziskin and Ziskin	1940				
Lennox	1934				
Metrakos <i>et al.</i>	1954				
Mayer-Gross <i>et al.</i> (p. 63)	1954				
Wallin (p. 383)	1949				
Falk <i>et al.</i>	1945				
Bridge (p. 488)	1949				
					No decided deterioration.
					No deterioration after 2 years.
					Long continued bromides and barbitones do not cause deterioration.
					Number of seizures seems to have no effect on deterioration.
					Relationship to deterioration concomitant not causal.
					Mentally defective epileptics nearly always primary oligophrenics.
					In a survey of 85 institutional epileptic defectives over 10 years, no consistent fall in I.Q. shown except 3 psychotic cases.
					Epilepsy not necessarily associated with retardation or deterioration.

E. EFFECTS OF SEIZURES ON MENTAL STATE AND ON THE BRAIN

A detailed study of 73 patients with "massive spasm" (sometimes called "lightning spasm" or "Blitzkrampfe" seizures) shows that 38 were severely retarded and 66 showed some retardation (Druckman and Chao, 1955). Quotations were given from numerous other authors, all of whom agree that "massive spasm" patients show associated mental retardation (Muskens, 1928; Buchanan, 1946; Yannet *et al.*, 1949; Lennox and Davis, 1950; Kellaway, 1952; Gibbs and Gibbs, 1952; Gibbs, Fleming and Gibbs, 1954).

Hodskins and Yakolev (1931), are cautious in associating mental deterioration with cases only showing evidence of "widespread cerebral atrophy"*. Herd (1930, p. 101), opines that "there are few (epileptics) in whom there are not some amounts of mental deterioration when, that is, the fits are fairly frequent and persistent", and Wallin (1949, p. 368), finds dementia produced by severe, frequent and long-continued grand mal.

* Clarke and Clarke (1958, p. 202): "So many tests (of brain damage) exist that as we are primarily concerned with investigations of M.D.s it will be desirable to shorten our discussion of tests in general by referring to recent descriptive summaries such as those of Yates (1954) and Shapiro (1951, 1952, 1953, 1954). Most of them are methodologically poor and many have inadequate and unstandardized scoring systems.

"Yates (1954) observes 'It is doubtful whether any aspect of psychological testing has been more inadequately treated than the diagnostic assessment of brain damage'".

[Also] (p. 206) "... theoretical uncertainties affect them ..."

Here again we have divergent schools of thought, since Lennox (1946, p. 53), champions the view that "mental deterioration occurs in only a minority of patients suffering from convulsions" and discredits the alleged damage by grand mal. The figures quoted in the following tables were given by Lennox in a personal communication to Bridge (1949, p. 49):

TABLE IV

*Effect of Total Number of Major
Convulsions on Intellectual
Abilities of 536 Individuals
Normal at Birth*

Total Seizures		Mentally Normal (Per cent.)
1- 9	..	92
10- 99	..	82
100-299	..	68
300-999	..	61
1,000 and over		45
Average	..	65

TABLE IVA

*Effect of Duration of Epilepsy on
Intellectual Abilities*

Duration in Years		Mentally Normal (Per cent.)	Severely Deteriorated (Per cent.)
0- 1	..	77	6
1- 4	..	72	9
5- 9	..	62	13
10-14	..	52	15
Over 15	..	50	20

(Tables adapted from *Epilepsy and Convulsive Disorders in Children* by E. M. Bridge, copyright 1949 by McGraw-Hill Book Co., Inc., N. York).

Lennox (1954) considers that brain damage is the factor of importance in determining intellectual level and adds that the number of seizures seems to have little or no effect, which point of view is supported by Penfield and Erickson (1941, p. 551), Fetterman and Barnes (1934), Dawson and Conn (1929), Sullivan and Gahagan (1935) and de Haas (1958, p. 79). Tylor-Fox (1950) seems to waver between the two schools: "The general conclusion is that a high incidence of major fits is the important factor in deterioration . . . some witnesses consider very frequent petit mal to be even more prejudicial . . . (but) . . . a recent search for deterioration in institutionalized patients produced surprising evidence of its absence."

Evidence from damage or deterioration caused by induced seizures (E.C.T.) suggests by analogy that natural convulsions may in fact produce similar results (Henderson and Gillespie, 1956, p. 421; Bridge, 1949; Mayer-Gross *et al.*, 1954, p. 383; Penfield, 1933). The possible nature of such damage has been discussed freely in the literature. The W.H.O. report (1957, p. 13) accepts that deterioration results from "status epilepticus and from many frequent convulsions".

Patients with brain damage (especially to the frontal and occipital lobes) tend to show irregularities similar to those described (*supra*) for epileptic subnormals (Wilkie, 1953, p. 70; Goldstein, 1939). Conversely we may suggest that general quantitative defects found in these individual subnormals may possibly indicate damage to cerebral tissue. This damage may be caused by vascular spasm in the ictal and post-ictal periods, leading to cerebral anoxia (Scholtz, 1951; Jung, 1949; Ruf, 1952; Hill, 1958; Echlin, 1940; Bourne, 1955). The W.H.O. report (1957, p. 13) considers that certainly status and probably many and frequent convulsions could lead to "oedema and vascular stasis progressing to various lesions in a wide and deep region that may involve the deep terminal lobe structures, the piriform cortex and parts of the inferior surface of the frontal lobe".

From observations reported by Grayzel (1934) and Terplan (1937) it seems probable that "severe grades of hypoglycaemia that remain untreated for some

time can result in injury to nerve cells and gross defects of the brain . . . that in time become a background for true epilepsy" (Bridge, 1949, p. 16).

Penfield and Erickson (1941, p. 199) pointing out the extreme variation of seizure tolerance shown by the individual, devote much time to this neurosomatic deterioration and mention that Hodskins and Yakolev (1930) have "presented cases and photographs illustrating . . . progressive deterioration over a period of years, ending in dementia", but they consider that "to date (1941) no significant relationship has been shown to exist between the severity and frequency of the attacks and the mental condition of the patient" (p. 552).

Finally, however, it does not seem that even definitely ascertained brain lesions causing intellectual defect need imply permanent deterioration (Henderson and Gillespie, 1956, p. 526). Penfield and Jasper (1954, p. 279) mention that it would seem that "a simple excision of non-functioning shrivelled gyri on the border of a central zone of complete destruction of the right hemisphere . . . converted what looked like a degenerating imbecile into a happy though somewhat retarded boy. At 8 years of age this case had a mental age of 6 years and an I.Q. of 69—thus comparing very favourably with many samples of 'deteriorated epileptics'."

F. HEREDITARY FACTORS IN THE ASSOCIATION OF EPILEPSY AND M.D.

A great deal of consideration has been given to the possibility of a hereditary factor in the association of epilepsy and mental deficiency.

Table V shows figures by various investigators which have been used with other evidence to formulate theories—at the moment, if potentially fruitful, nevertheless somewhat speculative.

TABLE V

Investigator(s)	Date	Comments			
Gowers	1881	30 per cent. of epileptics in the literature show a hereditary factor. 35 per cent. of own epileptic patients showed evidence of neurotic inheritance.			
Wallin (p. 355) ..	1917	Quotes figures by 9 workers:			
Investigator	Cases	%	Investigator	Cases	%
Reed	700	2	Hamilton ..	980	50
Eccheverria ..	306	26	Spratling ..	1,070	56
Gowers	2,222	40	Thom	157	80
Althaus	?	41	Krapelin ..	?	87
Hughes-Bennett	?	41			
(see comment by Wallin <i>infra</i>)					
Burr	1922	621 cases of serious nervous and mental disease in relatives of 1,449 epileptic patients. Effect heredity rarely direct and specific but indirect and general.			
Myerson	1925	Says heredity of epilepsy not proven.			

In the following cases the incidence of epilepsy in the families of epileptic propositi and of normal controls have been investigated and compared:

Investigator(s)	Date	Cases	Family History of Epilepsy		Comments
			Epileptic Propositi	Normal Control	
Brain	1926	200	28%	10%	
Stein	1933	1,000	18.1%	4.6%	
Himmler	1937	1,000	13%	of all relatives.	
			8%	of immediate family.	
Conrad	1937	?	4.4%	c. 0.6%	Incidence of epilepsy in children of epileptics.
			67 per cent. (idiopathic 86 per cent.) uniovular twins from whole institutionalized epileptic population of Germany were themselves epileptic.		
Alström	1950		No history in 889 of 897 cases. Critical attitude to all previous work after investigations on out-patient epileptics.		
Lennox	1951		20%		
Ounsted	1952	337	Genetic factors clearly established.		
Sal y Rosas	1953	Many	17%	7%	Institutionalized epileptics.
			23%		Symptomatic epileptics.
			29%		Idiopathic epileptics.
Lennox	1953	4,231	and their 20,000 parents, siblings and children.		
			3.6% if no lesion in propositi.		
			1.8% if lesion found in propositi.		
			(These percentages are normal for population)		
Metrakos <i>et al.</i>	1954	?	20%	2.3%	Centrencephalic.
Tenny	1955	765	43%		
Halstead	1957		20%	parental.	
			16%	second degree relatives.	
			10%	more distant relatives.	

Of the figures prior to 1917, Wallin (1917, p. 355) says: "When the percentages vary from 2 per cent. to 87 per cent. it is doubtful whether studies of this character have any scientific value."

Subsequent work, however, seems to have been on a much more carefully considered basis, and also modern knowledge of genetics has enabled fresh angles of approach. Siding with Wallin against a general hypothesis of the hereditary association of epilepsy with mental defect is Penfield (with Erickson, 1941, and with Jasper, 1954, p. 31) who does not favour the term "genetic epilepsy" which he quotes Lennox (1945) as using to imply that centrencephalic seizures are largely due to hereditary predisposition. Penfield and Erickson (1941, p. 305), further refer to the "theory of polymorphism . . . the inheritance of a unit factor which may predispose to the development of different neuropathic disorders in successive generations" which can neither be wholly proved nor disproved, though Penrose (1949, p. 199) states categorically that the polymorphic theory must be rejected, and Clarke and Clarke (1958, p. 128) that the evidence against it is impressive (Kallman *et al.*, 1941). A discussion of the question occurs in the American Medical Association Committee for the investigation of sterilization (Myerson, 1935).

For the contrary view, Lennox (1941) considers that his own studies "indicate that congenital mental deficiency and the heredity of epilepsy may be linked together and Mayer-Gross *et al.* (1954, p. 63) selects work mainly in Germany (Juda, 1934; Myerson and Boyle, 1941; Luxenburger, 1933; Brugger, 1928; and the classic Conrad, 1937, p. 373) to opine that there is "almost certainly some causative factor in common between idiopathic epilepsy and mental defect". Work done on twin subjects (Juda, 1939; Smith, 1930) might

be added in evidence, with the warning that investigations with twins are inevitably carried out in a homogeneous environment which may influence such findings as these (Hogben, 1941, p. 147; Newman *et al.*, 1937).

G. THE EFFECTS OF MEDICATION

It is sometimes suggested, especially by teachers of retarded epileptic children who see the practical results of efforts by the latter to apply their mental processes to academic tasks, that medication has a damaging effect. Lennox (1934) doubts this, saying that "in at least the majority of cases, the long-continued use of phenobarbitone and bromides does not affect the mind even after years of continual treatment". Other workers also claim that no "harmful" effects occur with continued medication with various anti-convulsants (Paskind, 1934; Fetterman and Barnes, 1934; Somerfield-Ziskinds, 1940; Heppenstall and Greville, 1952, p. 178; Bridge, 1949, p. 487). Heppenstall and Greville comment that the EEG pattern of children in whom sedative anticonvulsants had induced sleep or drowsiness were characteristic of those to be found in normal sleep or drowsiness respectively.

There is complete agreement that anticonvulsants do in fact nearly all produce characteristic side reactions: "apathy, drowsiness, sluggish mentality, ataxia and slow speech" (phenobarbitone) (Grinker, 1922), "drowsiness and lethargy" (phenobarbitone, Primidone, Diamox, Tridione), "drowsiness which often limits use" (methoin), "drowsiness and dream-like states" (Milontin) (Merritt, 1958). To go more deeply into the cause of the dulling is perhaps out of place in this Review, but the W.H.O. report (1957, p. 30) quotes that "most of the commonly used (anticonvulsant) drugs have a general depressant effect on neurone activity, probably by interfering with their energy-producing chemical reactions" (McIlwain, 1955).

On the other hand it is reported that "luminal accentuates the abnormal picture . . . characteristic of the 'genuine' epileptic" and that even normal persons who take this sedative will begin to show the same type of reaction in the Rorschach test (Stauder, 1938). Luminal and allied drugs have also been considered to have "a distinctly stultifying effect on the mind and will accentuate rather than relieve the abnormalities of personality" (Kimball, 1939, p. 553). Without pretending to any medical knowledge, many teachers of epileptic children will support these statements from observation over long periods. "These drugs", says Lennox (1934), "will of course produce somnolence and apathy . . . but that is obviously a temporary matter." But somnolence and apathy, especially over years of time, can play havoc with a child's efforts to learn and with his will to want to learn. As a teacher reasonably said: "The effect may be only temporary, but the children are only temporarily in my classroom."

Finally attention may be given to the possibility of *improvement* of mental state by medication. Reports of an increase in I.Q. observed after administration of sodium phenytoin (dilantin, epanutin) (Fabing, 1940; Twitchell-Allen, 1940) seem to have received no further confirmation, and one tends to agree that these observations may have been made as a result of the control of convulsions and removal of the toxic effects of previously used drugs (Penfield and Erickson, 1941, p. 554), but another interesting experiment has suggested the possibility of using massive doses of glutamic acid to raise the sugar metabolism of the brain (Albert, Hoch and Waelsch, 1946; Levinson, 1955, p. 88; Zimmerman *et al.*, 1948) and as a catalyst for the formation of acetylcholine (Lombard *et al.*,

1955). Once more conclusive figures are not available, though summaries and reviews of this research to date have been published by Milliken and Standen (1951) and Lombard, Gilbert and Donofrio (1955).

H. EVIDENCE FROM EEG PATTERNS AND PATTERN-VARIATION

The general consensus of opinion of those who have worked in the field of electroencephalography and mental testing or intelligence measuring is that there is no correlation to be found between the I.Q. and any characteristic of the EEG (Walter in Hill and Parr, 1952, p. 219; Lindsley, 1939; Jasper, 1937; Kreezer, 1936, 1939; Ellingson *et al.*, 1957; Henry, 1944).

An exception is quoted by Hill (1952): "Many demented patients have normal records. On the other hand, others have a slow alpha rhythm (6-8 c/s) which blocks poorly to visual attention . . ." Greenblatt, Levin and Attwell (1945) found that "psychometric methods were more reliable than the EEG in diagnosis of brain damage, but when both methods were used together, 91 per cent. of cases of abnormal findings by both methods had clinical evidence of brain damage". Similarly Hill (1952) says that "where mental deficiency is associated with epilepsy from birth, gross abnormalities in the EEG are the rule". He points out that the EEGs of many epileptic children show bursts of spike and wave or other paroxysmal normal activity indicating subclinical epileptic interruption with consciousness which "gives little opportunity for the utilization of the brain function for learning or mental development".

Sometimes it has been reported that a greater incidence of slow waves is to be found in the EEGs of institutionalized epileptics than in the extramural types (Bellinson and Cowie, 1947), but more recent work has tended to establish the opinion that slow EEG activity is related to maturation disorder rather than to epilepsy (W.H.O., 1957, p. 21). Corbin and Bickford (1950) give a catalogue of frequencies to be found at successive ages in normal children, and information of a similar nature occurs in Gibbs and Gibbs (1952), as well as in Lindsley (1939).

Turning further away from normality to epileptic dementia, a "correlation between clinical evidence of the severity of the dementia and EEG slowing" has been reported (Weiner and Schuster, 1956) and typical waveforms which have been said to appear in lipidosis and acute encephalitis "may foreshadow a limited return to the concept of the EEG pattern-representation of cerebral disease" (Cobb *et al.*, 1952).

As yet the interpretation of the EEG record—in fact the recording of the EEG record—is still in a very young stage. There is obviously more on the record than can be translated at present. Also the practical difficulties of getting clear, fool-proof recordings, free from muscle artefact, and of ensuring that the pens in fact record what they purport to record, make work in this field very difficult and hazardous. Rewarding work has however been done on the nature of electrical changes during mental activity and the patterns they form and the interpretation of these patterns and the way they vary (Mundy-Castle, 1951, 1957). From this it would seem to be a logical sequel to investigate the abnormalities, judged by such criteria, shown during the attempted working of mentally defective or mentally retarded brains.

J. SUMMARY

1. From such studies as have been made and their findings published, we get a very indefinite picture of the level of intelligence of epileptics and its relationship to epilepsy.

2. Whilst there is little evidence to show that epileptics *per se* have a lower degree of intellect than non-epileptics, certain groups of epileptics—notably institutionalized cases—reveal mental shortcomings and in some cases progressive deterioration ending in extreme dementia. The nature and aetiology of these cases invites research.

3. Largely owing to the extreme seizure-tolerance variation shown by different individuals, there is as yet insufficient evidence to show to what extent and in what manner the incidence and persistence of epilepsy is responsible for mental deterioration, though it would appear that convulsions, especially if frequent, severe and of long-standing do in fact cause actual cell-damage in the C.N.S. and in the brain.

4. From time to time claims have been made to have found significant associations of epilepsy with mental deficiency and significantly large percentages of convulsive disorders in mentally defective populations. There is a field for research into the *qualitative* aspects of these claims.

5. A great deal of consideration has been given to the possibility of a hereditary factor in the association of epilepsy and mental deficiency, but the figures vary so much that there has been a complete review of the approach. Much recent work has been directed to investigations along lines of modern genetic theory.

6. Although it may be accepted that drowsiness and apathy induced by most anticonvulsant drugs disappears on reduction or withdrawal, it is obvious that intensive temporary effects are produced during the often prolonged periods of medication. Further research is indicated into the secondary effects of these drugs on the individual mental processes rather than on the general intelligence level of a group of patients.

7. There is as yet no recognizable connection between the EEG pattern of the normal or epileptic subject and any measure of mental capacity. The fact that EEG interpretation is in its infancy gives hope for the emergence in time of some relationship useful as a diagnostic factor.

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OBTAINING FACTOR SCORES ON THE WECHSLER ADULT INTELLIGENCE SCALE

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PROBLEM

ELSEWHERE (3) it has been argued that, when reporting a subject's results on the WISC (5), it is preferable to give them in the form of scores or intelligence quotients on orthogonal factors than as Verbal and Performance I.Q.s since the latter overlap in a rather arbitrary fashion. In this study a similar recommendation is implied when dealing with a subject's results on the WAIS (6) and the problem is to indicate how factor scores on this test can be obtained.

PROCEDURE

A factor analysis of the correlation matrix for the (18-19) year group (6), omitting the *Information* subtest which is seldom administered at this Institute, was performed using the Lawley Maximum Likelihood Method of analysis (4). After two factors had been fitted the residuals were tested and found not to be significant ($\chi^2=24\cdot9$; d.f.=26). The factors were then rotated so that the first passed through the Vocabulary subtest. This rotation is the one most acceptable to my clinical colleagues, who then label the factor "verbal-intellectual, (vg)". The second factor, orthogonal to it, is labelled "space-performance (sp)". The unrotated and the rotated loadings are given in Table I.

TABLE I
Factor Loadings for (18-19) Age Groups

	Unrotated			Rotated	
	I	II	h^2	I	II
1. Comprehension ..	·746	—·217	·604	·777	·011
2. Arithmetic	·715	—·114	·524	·717	·100
3. Similarities	·834	—·169	·724	·847	·082
4. Digit span	·637	—·163	·432	·657	·030
5. Vocabulary	·874	—·268	·836	·914	·000
6. Digit symbol	·697	—·066	·490	·686	·141
7. Picture completion ..	·773	·231	·651	·672	·447
8. Block design	·727	·391	·726	·609	·596
9. Picture arrangement	·697	·207	·529	·606	·402
10. Object assembly ..	·690	·431	·661	·533	·614
Per cent. variance ..	55·51	6·26	61·77	50·47	11·30

All subtests, Verbal and Performance alike, are seen to have high loadings on the first rotated factor, while the Verbal subtests together with the Digit Symbol subtests have negligible loadings on the second factor.

The correlation matrices for the (25-34) and the (45-54) age groups were now considered. Here the hypothesis was set up that two factors would be sufficient to account for the covariance of the tests and that the pattern of loadings would be similar to that of the rotated loadings for the (18-19) age

group. In other words it was postulated that the first six tests would have zero loadings on the "space-performance" factor. This hypothesis was tested by a new maximum likelihood method of analysis described by Lawley (1) and discovered independently by Howe, and by others (2). The great advantage of this new method is that the estimated loadings do not require rotation.

The results of the analyses are given in Table II. The residual matrices after two factors have been fitted were not tested for significance as the test involves laborious calculations (a programme for doing it on an electronic computer is in hand). When the loadings in Table II are compared with the rotated loadings in Table I it is seen that for all three age groups the pattern is closely similar. In each case all subtests have high loadings on the "verbal-intellectual" factor, Vocabulary, Similarities and Comprehension topping the list. For the "space-performance" factor the highest loadings for each age group are for Object Assembly and Block Design. The Verbal tests in every case have loadings on this second factor which are virtually zero while the loadings for the Digit Symbol subtest are negligible.

TABLE II
Factor Loadings for (25-34) and (45-54) Age Groups

Test	(25-34) Years			(45-54) Years		
	I	II	h^2	I	II	h^2
1. Comprehension ..	.776	.052	.605	.827	.042	.686
2. Arithmetic ..	.657	.147	.453	.755	.177	.601
3. Similarities ..	.804	.018	.647	.796	.073	.639
4. Digit span ..	.569	.086	.331	.609	.173	.401
5. Vocabulary ..	.921	-.042	.850	.910	-.017	.828
6. Digit symbol ..	.641	.170	.440	.690	.191	.513
7. Picture completion ..	.677	.364	.591	.726	.327	.634
8. Block design ..	.606	.551	.671	.586	.556	.653
9. Picture arrangement	.684	.311	.565	.708	.232	.555
10. Object assembly ..	.487	.577	.570	.567	.533	.606
Per cent. variance ..	47.94	9.29	57.23	52.56	8.59	61.16

REGRESSION WEIGHTS FOR FACTOR SCORES

In virtue of the similarities between the factor patterns for the three age groups it was decided to average the three correlation matrices (using the z-transformation) and to average the three sets of factor loadings and find one set of regression weights (4) for estimating scores on the two factors. These are given in Table III, the values in brackets falling below the 5 per cent. level of significance. Below the true weights approximate weights (to simplify the calculations) are indicated. Below them again the scaled scores for a hypothetical subject are given. These scores are expressed in standardized form by subtracting 10 from each and by dividing the remainder by 3, the standard deviation of the scaled scores.

Examination of the regression weights, Table III, shows that by far the

TABLE III
Regression Weights for Estimating Factor Scores

Tests	1	2	3	4	5	6	7	8	9	10
Factor "vg" ..	.16	.09	.19	.08	.44	.08	.06	(.00)	.04	(.00)
Factor "sp" ..	-.16	(-.02)	-.13	-.04	-.48	(.01)	.22	.49	.15	.42
Approximate Weights										
Factor "vg" ..	.2	.1	.2	.1	.4	.1	.1	0	0	0
Factor "sp" ..	-.2	0	-.1	0	-.5	0	.2	.5	.2	.4
Subject's Scores										
Scaled score ..	13	12	10	7	16	16	8	13	10	14
St. score ..	1	0.7	0	-7	2	2	-0.7	1	0	1.3

most important subtest for estimating the "vg" factor score is Vocabulary; it is followed by Similarities and Comprehension. For estimating the "sp" factor Block Design and Object Assembly have relatively high positive weights, but to counteract the high "vg" content of these tests a high negative weight for Vocabulary is required. (Digressing for a moment it is seen that should a shortened form of the WAIS be required the regression weights indicate the subtests which should be retained.)

To illustrate how factor scores are calculated we will use the standardized scores given in the last row of Table III. These scores are multiplied in turn by the corresponding regression weights, rows one and two (or rows three and four) of the table, and the results are added. In this way the "vg" factor score is found to be 1.181 and the "sp" factor score to be -0.192. The variances of the factor scores can also be found (4), and for the regression weights given never have to be recalculated. For the factors in question they are 0.92 and 0.65, and as the covariance between the factor scores is 0.0787 the correlation between estimated factor scores is 0.10. To express the factor scores as I.Q.s they are restandardized. They then become $1.181/\sqrt{0.92}$ and $-0.192/\sqrt{0.65}$, namely 1.229 and -0.239 for the "vg" and "sp" factors respectively. Expressed as I.Q.s these are $100 + 15 \times 1.229 = 118.4$ and $100 - 15 \times 0.239 = 96.4$. These differ by 22 points of I.Q. Had the scaled scores been expressed as Verbal and Performance I.Q.s in the ordinary way, assuming the subject to be in the 18-19 age range, the values 101 and 115 respectively would have been obtained. These I.Q.s are almost the reverse of those obtained when the factor scores are used and could be misleading should the labels Verbal and Performance be taken literally. The discrepancy between the results obtained from factor scores and conventional usage is caused largely by including the subtest Digit Symbol amongst the Performance tests: the factor analysis and regression weights strongly indicate that it does not belong there.

SUMMARY AND DISCUSSION

Factor analyses of the correlation matrices given in the WAIS manual are reported and sets of regression weights are given for estimating "verbal-intellectual", and "space-performance" factor scores. The variances and the covariance of the estimated scores are given and it is demonstrated how to convert a S's scaled scores on the test into factor score I.Q.s. It is argued that the latter are preferable to the conventional Verbal and Performance I.Q.s for use in clinical work.

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SOME NEUROLOGIC AND PSYCHIATRIC ASPECTS OF BILATERAL INTERNAL CAROTID OCCLUSION

A CASE REPORT

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ALTHOUGH the syndrome of internal carotid artery occlusion was first described by Ramsey Hunt in 1915, the neurological complications were not fully appreciated until recent years. Internal carotid occlusion has now been intensively studied, and the criteria for its diagnosis well defined (Webster *et al.*, 1956; Shapiro and Peyton, 1954; McGuire and Jaeger, 1955; Smyth, 1954; Moniz, Lima and de Lacerda, 1937; Hultquist, 1942). Among its clinical manifestations psychiatric features have been mentioned: they range from so-called mental aberrations (Eisenberg, 1955), personality changes, emotional instability and memory loss (McGuire, 1955), to frank dementia (Fisher, 1941). Little attention, however, has been given to the problem of the relationship of bilateral internal carotid occlusion to dementia, and few attempts have been made to document by psychometric testing the degree of intellectual impairment. It is for this reason that a case of bilateral internal carotid occlusion is now reported.

Fisher (1941) reported a case of senile dementia associated with bilateral occlusion of the internal carotid arteries. It was suggested that the clinical picture of dementia was the result of long-standing but mild cerebral ischemia and that the involvement of the frontal and anterior temporal regions in senile atrophy might be explained on the basis of inadequate cerebral circulation through the internal carotid arteries. Following this case report, further studies were made. In an analysis of 45 cases of occlusion of one or both internal carotid arteries, Fisher (1954) discovered 12 cases of dementia. This prompted him to say that "it would appear that in the long history of the study of senile dementia the state of the carotid vessels carrying the major portion of the blood supply to the brain has never before been investigated". It was inferred that such occlusions are a frequent cause of senile dementia, and the findings of Freyhan, Woodford and Kety (1951) that there is an unexplained 25 per cent. reduction in cerebral blood flow in arteriosclerotic dementia and senile psychosis were used to support this contention.

It is extremely difficult to state the incidence of dementia in bilateral internal carotid occlusion. In a series of proven cases of carotid occlusion, 35 in number, admitted to Neurological Institute from 1949 to 1957, Hass and Goldensohn (1959) found three examples of organic mental syndrome, two of whom had unilateral carotid artery disease. Two other patients had bilateral carotid occlusion but showed no signs of frank intellectual impairment. Reporting one case of bilateral involvement, Clarke and Harrison (1956) reviewed all such cases in the literature, a total of 69 patients. Twenty-nine per cent. showed mental changes, but only 10 per cent. of the total group was

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severely impaired. They also report one patient with bilateral pyramidal signs, but no mention is made of pseudobulbar palsy in other reports.

Inasmuch as a neurological and psychiatric evaluation of bilateral internal carotid occlusion has not, to our knowledge, been reported in a detailed manner, it is considered of interest to discuss a patient in whom full psychiatric and psychometric investigation failed to detect the occurrence of dementia.

CASE REPORT

This fifty-three year old married woman was admitted to the Maudsley Hospital on 10 October, 1958, from an observation ward. During the preceding six years she had complained of buzzing in the head; three years ago, the buzzing had become worse and associated with fatigue, dull headaches and a gradual narrowing of her domestic and social interests. At this time her husband observed that she occasionally laughed and cried for no apparent reason. She was seen by her practitioner and found to be hypertensive. In September, 1958, because of tingling in her fingers, incipient weakness of the left arm, general apathy and worsening of her emotional lability, she was referred to a university hospital out-patient department, where admission was advised. Examination revealed a blood pressure of 190/100 mm. Hg, an enlarged heart and moderate weakness of the left arm and leg with ipsilateral hyperreflexia. Plantar responses were flexor, and there was no sensory impairment. An electrocardiogram demonstrated slight depression of ST segments of V5 and V6; but other studies—including skull X-rays, lumbar puncture and electroencephalography—were normal. Within two weeks power of the left hand had been regained, and the patient was walking about the ward with assistance. Discharged home 1 October, 1958, to be followed in the out-patient department, the patient was diagnosed as suffering from arteriosclerotic dementia. Over the subsequent three weeks the left hemiparesis became worse, the emotional lability more marked and speech slurred. Grip of the right hand was weak, and urinary incontinence occurred. Because of the deterioration, the patient was admitted to an observation ward on 22 October, 1958. Examination there revealed a blood pressure of 200/100 mm. Hg, a left spastic hemiparesis, and a left extensor plantar response. Early hypertensive retinopathy, dysarthria and emotional incontinence were also present. She was moderately depressed in mood, but the mental state was otherwise normal. A week after admission a left Horner's syndrome was noted. Tone was increased in both arms, and an increased jaw jerk was evident. The diagnosis of arteriosclerotic dementia was questioned, and the patient was transferred to the Maudsley Hospital for further evaluation.

At the Maudsley Hospital, in addition to the previous findings, it was noticed that the radial arteries were full, equal and not hardened to palpation. The pulsations of the dorsalis pedis and the posterior tibialis arteries were reduced, more so in the left extremity.

Psychiatric Examination. The patient was emotionally labile, exploding into laughter and crying inappropriately and at the slightest provocation. Speech was slowed and slurred, but not circumstantial or perseverating. She admitted feeling depressed which she attributed to ill health, the recent marriage of a son to a non-Catholic and the death of a young sister. Nevertheless, guilt, retardation and sleep disturbance were not present. Misinterpretations, hallucinations, ideas of reference and compulsive phenomena were not elicited. Orientation was unimpaired. Memory for past, recent past and present was good, but attention and concentration were somewhat impaired for arithmetic, serial sevens and the "cowboy story". She was fully aware of her illness.

Neurological Examination. Visual acuity was good. Visual fields were intact on confrontation and to perimetry. Fundoscopy demonstrated arteriolar narrowing and arteriovenous nicking. The left pupil was 3 mm. smaller than the right, and a left ptosis of 2-3 mm. was present. Facial sensation and corneal reflexes were intact. The jaw jerk was increased. Hearing was unimpaired. Speech was slurred. The left arm was held in flexion and adduction, with a flexion deformity of the left hand and generalized weakness of that extremity. The right arm showed slightly reduced power. Resistance to passive stretch was increased, more so on the left. There were errors of two-point discrimination and stereoagnosis on the left. The left leg was externally rotated, its power reduced, and its tone increased. There was slight weakness of the right arm. On the left the tendon reflexes were increased, and the plantar response was extensor.

Laboratory Investigations. The urine was normal; B.U.N. was 30 mg. per cent., and the Wassermann and Kahn reactions were negative. An electroencephalogram was normal. Chest X-ray demonstrated left ventricular hypertrophy. Skull X-ray showed only calcification of the carotid syphons. A left carotid arteriogram displayed almost complete obstruction involving the proximal 1.5 cm. of the internal carotid, with filling of the carotid syphon through an anastomosis of the internal maxillary and ophthalmic arteries. Later a right carotid arteriogram demonstrated marked stenosis of the internal carotid artery due to atheroma. The degree of narrowing of the lumen was less than on the right, and there was slight filling of the cerebral vessels. On vertebral arteriography the basilar arteries and its branches were well filled. In addition there was some filling of the left internal carotid artery and its branches.

Psychological Testing. This was done to assess if the patient was demented. The Wechsler-Bellevue Form I verbal score was 78. Verbal subtests and weighted scores were: comprehensive 5, arithmetic 3, digit span 4, similarities 3, and vocabulary 7. The Raven's Matrices score was 13, indicative of an I.Q. of 79-89. A general appraisal of intellectual function, based on testing and on the family's report of pre-morbid performance, was thought to substantiate the opinion that the present level of dull average intelligence was consistent with what was known of her previous abilities. On the Inglis Memory tests the patient obtained an auditory recall score of 21 and a visual recall score of 11. It was believed that the results of the visual recall test gave a fairly certain indication of normal memory function. The Walton-Black modified learning test score was 39, indicating brain damage. In the Archimedes spiral test after-images were observed in three-fourths of the presentations. Two months after the initial testing the patient was retested with the Raven's Matrices and the Wechsler-Bellevue Form II. Results were consistent with the hypothesis that the first test results were reliable and that there had been no measurable deterioration over the eight week interval.

Progress. After admission the patient was given physiotherapy. Partial return of function of the left arm was obtained, and with assistance she started ambulation. The neurological status remained unchanged, except for the incomplete Horner's syndrome which partially cleared, leaving only a slight ptosis. On 22 December, 1958, the patient was transferred to another hospital for consideration of neurosurgical treatment. It was thought that further neurological deficit could possibly be averted by reconstruction of the right internal carotid artery at the atheroma (Edwards and Rob, 1956; Eastcott *et al.*, 1954). Several days after transfer the patient developed pulmonary oedema. Because of hypertensive cardiovascular disease it was thought that she was not a suitable candidate for surgery, and treatment with anticoagulants was begun. The patient was discharged essentially unchanged on 5 March, 1959, to a chronic hospital.

COMMENTS

The findings in this case satisfy the clinical and laboratory criteria for the diagnosis of bilateral internal carotid artery occlusion. The patient had a number of the prodromata, including tinnitus, paresthesiae, headache; and she developed then a left hemiparesia, followed by weakness on the right side and pseudobulbar palsy. In addition she had a Horner's syndrome. There was no history, however, of transient monocular blindness. The diagnosis was confirmed by carotid and vertebral arteriography, and the patient's progress was observed for several months.

During the early days of her illness the patient displayed some narrowing of her general interests, reduction in initiative, as well as evidence of depression. But there was no evidence of impulsiveness, anxiety, irritability, hallucinations or delusions, so often described in this syndrome. The depressive features, although outstanding, were not new, for the patient had been depressed before on a number of occasions, usually in relation to unfavourable external events, and at the time of her illness she was pre-occupied with family problems and her failing health. It has been observed that patients who have been depressed before the onset of a cerebral vascular disturbance become more depressed after its occurrence (Chason, 1958; Clarke and Harrison, 1956). Tourney, Cohen and Gottlieb (1958) studied 24 patients with occlusive vascular disease, demonstrated by arteriography. They found no relationship between localization of the lesion and mental symptom; and concluded that such symptoms were exaggerations of pre-morbid personality traits. Similar conclusions were reached from studies of the psychopathology of organic states (Weinstein and Kahn, 1955).

Memory loss and frank personality changes were never observed in this patient. Although initially regarded as demented because of her emotional incontinence, there was no evidence to support the diagnosis. After the bilateral pyramidal signs had been noted, the emotional incontinence was recognized to be a manifestation of pseudobulbar palsy, caused by bilateral infarction of the internal capsule. Psychological testing corroborated the clinical opinion that the higher intellectual functions had not been impaired. Mental deterioration,

however, has been reported in a number of cases of bilateral carotid artery occlusion. Paillas and Bonnal (1954) found signs of dementia in 6 of their 21 patients. Johnson and Walker (1951) recorded it as a finding in 15 per cent. of their patients with unilateral internal carotid occlusion. Chason (1959) in his review of 24 cases of cerebral vascular occlusive disease discovered two patients with bilateral internal carotid occlusion. One was considered to be impaired intellectually, and on the basis of the Wechsler-Bellevue and Benton Visual Retention tests, a deficit in visual memory and organization was apparent. The second patient, mildly intellectually impaired, was not evaluated by psychometric methods.

It now appears that the association of bilateral internal carotid occlusion and dementia is not as clear as initially suspected. No longer can it be inferred that dementia necessarily occurs. Since his initial neuropathological studies, Fischer (1959) has also encountered bilateral occlusion with relatively good preservation of the mental state. In one of his cases both internal carotid arteries and one vertebral artery were completely occluded when examined post-mortem, but the patient was so free of any complaint that his wedding had been set for a date only two or three days after the onset of his stroke. It is now apparent that the manifestations of bilateral carotid occlusion constitute a wide spectrum of signs and symptoms, and that there is little correlation between the site of the vascular occlusion and the neurological deficit. This fact is illustrated by the present case report: the patient's main weakness was on the left side of the body, whereas the right internal carotid was still partially patent. Such variations in the syndrome depend on the form of the Circle of Willis, the adequacy of the cerebral circulation, and the maintenance of blood pressure, sufficient for perfusion of blood to effective cerebral circulation (Symonds, 1955).

The patient's illness was thought initially to be caused by general arteriosclerosis; later, it was believed that the diffuse neurological signs could best be explained by "*l'état lacunaire*", or hypertensive arteriosclerotic encephalomalacia. The presence of a Horner's syndrome, however, pointed to carotid occlusive disease, which was later proved by arteriography. The diagnostic significance of Horner's syndrome in internal carotid artery occlusion has recently been emphasized: O'Doherty and Green (1958) found a Horner's syndrome in 12 of their 18 patients with internal carotid occlusions. Walsh (1952) and Jaffe (1950) also comment on its association. It is generally believed that ischemia of the sympathetic neurons of the third order may result from such occlusions because of diminution of blood flow through the vasa nervorum coming from the carotid artery. Although not entirely reliable, this physical finding can be of assistance in establishing the diagnosis of carotid artery occlusion.

CONCLUSIONS

1. Bilateral internal carotid occlusion can present as pseudobulbar palsy with emotional lability, which strongly resembles dementia but should not be confused with it.
2. Dementia is not necessarily associated with bilateral internal carotid occlusion.

SUMMARY

A case report is presented of a 53-year old woman with pseudobulbar palsy and emotional incontinence resulting from bilateral internal carotid

occlusion. It is easy to confuse the emotional incontinence of pseudobulbar palsy with that of dementia. The incidence of dementia and other psychiatric features in bilateral internal carotid occlusion is discussed.

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FAMILY DATA CONCERNING THE HYPOTHESIS OF HEREDITARY PREDISPOSITION TOWARD ALCOHOLISM

By

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THERE is evidence of unduly high frequencies of alcoholism, psychopathy and criminality among the relatives of alcoholics. Åmark (1951) found a frequency of alcoholism among the brothers and fathers of 645 Swedish alcoholics to be about 25 per cent. (Fremming's estimate of alcoholism among 1,730 males from the Danish population being 3·4 per cent.). In a more recent study of family data on 1,000 patients admitted to a Canadian mental hospital that included 56 patients with alcoholism, the present author (Gregory, 1959) found a recorded history of excessive drinking among 23·2 per cent. of the fathers of the alcoholics, among 1·8 per cent. of the mothers, and among 4·2 per cent. of their siblings. Allowing for the age and sex of these siblings, it would appear that there was a lifetime expectancy of excessive drinking of at least 14 per cent. among the brothers of these alcoholic patients. These figures compare with a minimal estimated lifetime expectancy of alcoholism amounting to 1·6 per cent. of the total population, or at least 2·7 per cent of the corresponding male population of Ontario.

The increased frequency of excessive drinking among the immediate (male) relatives of alcoholics may be attributable to one of the following three hypotheses: (i) that there is a similar hereditary predisposition, (ii) that there is a direct (postnatal) transmission of faulty patterns of adaptation, (iii) that affected members of the same family unit share similar experiences in a pathogenic environment.

There are obvious difficulties in applying uniform criteria for the diagnosis of alcoholism, but the recorded frequencies of alcoholism amongst the relatives of alcoholics do not appear to conform with those expected under any hypothesis of simple Mendelian inheritance (whether dominant or recessive, autosomal or sex-linked). However, Åmark (1951) attributed at least part of the intrafamilial concentration of alcoholism in his study to hereditary factors, and Kallmann (1959) considers that various leads exist toward the eventual identification of a genically controlled biochemical basis for alcoholism. He goes on to suggest that the metabolic deficiency underlying compulsive drinking patterns may be traceable to one or more of the following components (found to be significantly different in alcoholic men): serum sodium, serum potassium, serum calcium, blood glucose, urinary creatinine, urinary hippuric acid, urinary sodium, and urinary chloride (Williams *et al.*, 1957). However, it is easy to confuse cause and effect, and these biochemical findings may be the result of excessive alcohol intake (or both may be caused by a third class of variable). In this connection, it would be interesting to know the frequencies with which such biochemical anomalies occur among different

classes of alcoholic and non-alcoholic relatives of patients with established alcoholism.

Another valid approach to this problem is to test the hypothesis that there is random genetic transmission of alcoholism within the sibships of alcoholics, regardless of possible environmental influences related to such objective factors as parental ages at birth, parental loss by death or permanent desertion, family size, birth order, ordinal position, sexes of siblings, and intervals between the patient and preceding and following siblings. In the present article, it is planned to illustrate this approach by extending the analysis of certain data on male alcoholics undertaken by Bakan (1949), and to test the preceding hypothesis with respect to family size, birth order, and ordinal position.

METHOD

Source of Data

Bakan presented data and statistical analyses of birth rank (birth order) on two samples of male alcoholics convicted of crimes involving the misuse of alcohol—chiefly “public intoxication”—in the State of Indiana. The data for Sample I consisted of distributions of birth rank and family size of 1,493 alcoholics, but there was no information showing both the birth rank and size of family for each subject, and the present author considers the data recorded for Sample I extremely suspect. Both the highest family size and the highest birth rank recorded for this Sample I amounted to only 10 (which in itself would be most unusual in so large a sample) and, since there were only 22 individuals recorded as coming from families having ten members, it is manifestly impossible that 42 of them should have been born tenth in birth rank. It is concluded that this observation completely invalidates the apparently very significant distribution of alcoholism according to birth rank in this Sample I.

Bakan's Sample II consisted of 110 alcoholics concerning whom both the birth rank and family size was recorded for each subject. The two samples were said to be independent and, with certain reservations, it appears worth while to examine this latter sample in more detail.

Analysis of Family Size, Birth Order and Ordinal Position

The method developed by Greenwood and Yule (1914) enables the calculation of corrected family sizes, and of expected frequencies of different birth orders, from samples taken through members of the sibships. The present author has described a simple extension of this method in order to estimate expected frequencies of different ordinal positions, and has discussed a number of possible sources of statistical bias in the application of these methods (Gregory, 1958).

RESULTS AND DISCUSSION

(a) Family Size

Table I shows the size of sibship and birth order of the 110 male alcoholics in Bakan's Sample II, and Table II shows the Greenwood-Yule reconstruction of the sibships of these alcoholics, with respect to corrected family size and birth order. There are three aspects of corrected family size that will be considered here—namely, the mean and modal size of family, and the percentage of only children.

TABLE I

Size of Sibship and Birth Order of 110 Male Alcoholics in Bakan's Sample II

		Size of Sibship (x)												Totals	
Birth Order		1	2	3	4	5	6	7	8	9	10	11	12	(O _x)	
1	..	..	10	9	8	1	2	3	1	—	—	—	—	34	
2	..	..	..	10	6	1	1	2	1	—	1	—	—	22	
3	..	..	..	..	9	4	3	3	3	1	—	—	—	23	
4	..	..	..	..	..	6	—	2	—	—	1	—	—	9	
5	..	..	..	..	..	1	3	—	1	1	—	—	—	6	
6	..	..	..	..	..	..	3	1	1	—	—	—	—	5	
7	..	..	..	..	..	..	..	3	1	—	—	—	—	4	
8	..	..	..	..	..	..	..	..	4	—	1	—	—	5	
9	..	..	..	..	..	..	..	..	..	—	—	—	1	1	
10	..	..	..	..	..	..	..	..	..	..	1	—	—	1	
11	..	..	..	..	..	..	..	..	..	..	..	—	—	0	
12	..	..	..	..	..	..	..	..	..	..	..	..	—	0	
Totals (F _x)		..	10	19	23	12	7	16	9	8	2	3	0	1	110

TABLE II

Greenwood-Yule Reconstruction of Sibships of 110 Male Alcoholics in Bakan's Sample II

Size of Sibship (x)	Frequency of Sibship Recorded in Sample of Patients (F _x)	Weighted Frequency (as would have been Obtained from Sample of Mothers) (F _x /x)	Expected Frequency of Each Birth Order (Summing F _x /x̄ from Bottom Upwards) (E _x)	Observed Frequency of Each Birth Order (O _x)	(O _x - E _x) ² E _x
1	10	10.0	37.13	34	0.30
2	19	9.5	27.13	22	0.94
3	23	7.67	17.63	23	1.44
4	12	3.0	9.96	9	0.09
5	7	1.4	6.96	6	0.13
6	16	2.67	5.56	5	0.06
7	9	1.29	2.89	4	4.51
8	8	1.0	1.60	5	
9	2	0.22	0.60	1	
10	3	0.3	0.38	1	
11	0	0.0	0.08	0	
12	1	0.08	0.08	0	
Totals	110	37.13	110.00	110	7.47

Characteristics of corrected family size (F_x/x̄)

Mode = 1
 Median = 1.90
 Mean = 3.42

Goodness of fit between expected and observed frequencies of birth order

$\chi^2 = 7.47$
 Degrees of freedom = 6
 $\therefore 0.20 < p < 0.30$

The corrected *mean size of family* is obtained by dividing the total number of subjects in the sample by the sum of the weighted frequencies (as would have been obtained from a sample of mothers)—i.e.: $\Sigma F_x \div \Sigma (F_x/x) = 110 \div 37.13 = 3.42$. This corrected mean family size is exactly the same as that obtained by the present investigator for his sample of alcoholics admitted to a Canadian mental hospital (Gregory, 1959).

In comparing the means and modes of live children ever born per married mother for about 50 large samples of British mothers (by year of marriage, age at marriage, and broad social status group), the present author found empirically that with a mode of one the mean did not exceed 2.6 in any instance (Gregory, 1958, Table VIII). The *mode* of one recorded in Bakan's Sample II, together with the corrected *percentage of only children* amounting to almost 27.0, might conceivably be due to the inclusion of some illegitimate subjects among the only children in this sample. However, the findings are again paralleled by a mode of one and corrected percentage of only children amounting to 25.8, among the present author's sample of alcoholics (Gregory, 1959), even after the exclusion of all subjects believed to be illegitimate. Comparable general population figures for only children amounted to less than 20 per cent., and there appears to be an unduly high frequency of only children among both the samples of alcoholics.

(b) *Birth Order*

Table II also shows the goodness of fit between expected and observed frequencies of each birth order, which corresponds closely with Bakan's findings (excluding the only children), and might have been expected by chance about once in four trials.

(c) *Ordinal Position*

Bakan compared observed and expected frequencies of three categories of ordinal position (eldest, youngest, and all other positions combined) regardless of family size. The present author has preferred to make comparisons between a greater variety of ordinal positions, for family sizes having four or more members, in the hope of decreasing sources of selective bias and increasing the sensitivity of the method (Gregory, 1958, 1959). The results of this analysis are shown in Table III, in which it may be observed that the frequency

TABLE III
Ordinal Position Among Alcoholics in Bakan's Sample II, from Sibships Having Four or More Members

Ordinal Position in Sibship for Alcoholics from Sibships Having Four or More Members					Expected Frequency (E_p)	Observed Frequency (O_p)	$(O_p - E_p)^2$ E_p
Eldest	..	..	..	..	9.96	7	0.88
Second born	..	..	..	..	9.96	6	1.57
Intermediate	..	..	..	..	18.16	18	0.00
Penultimate	..	..	..	..	9.96	9	0.09
Youngest	..	..	..	..	9.96	18	6.47
Totals	..	..	..	..	58.00	58	9.01

Goodness of fit for *ordinal position* in sibships having four or more members

$$\chi^2 = 9.01$$

$$\text{Degrees of freedom} = 4$$

$$\therefore 0.05 < p < 0.10$$

of youngest born from sibships having four or more members, was at least twice as great as that observed for either eldest, second born, or penultimate, and that a deviation of this magnitude could have been expected to occur by chance only once in more than 15 trials. This finding suggests a vulnerability to alcoholism among the youngest member of large families, but cannot be

regarded as definitely established, particularly in view of conflicting findings with respect to the vulnerability of the same ordinal position for other types of psychiatric disorder (Gregory, 1958, 1959).

SUMMARY

The hypothesis is stated that there is random genetic transmission of alcoholism within the sibships of alcoholics, regardless of possible environmental influences related to such objective factors as parental ages at birth, parental loss by death or permanent desertion, family size, birth order, ordinal position, sexes of siblings, and intervals between the patient and preceding and following siblings.

A method of testing this hypothesis, with respect to family size, birth order and ordinal position, has been illustrated by extending the analysis of data on 110 male alcoholics previously recorded by another author.

The corrected mean family size of 3.4 and modal family size of 1 are identical with those previously obtained by the present investigator for another sample of alcoholics. Empirically, a mode of 1 is not expected with a mean larger than about 2.6, and the corrected frequency of only children among both samples of alcoholics appears unduly high (over 25 per cent. of weighted frequencies in each instance).

The goodness of fit between observed and expected frequencies of each birth order was such as might have been expected on the basis of chance about once in four trials.

The observed frequency of youngest born from sibships having four or more members was at least twice that observed for either eldest, second born, or penultimate members. A deviation of this magnitude could have been expected to occur by chance only once in more than 15 trials.

These findings suggest that the vulnerability of certain individuals to alcoholism is not determined solely by random genetic predisposition, and further more extensive tests of the initial hypothesis appear justified.

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A PRELIMINARY REPORT ON THE USE OF SERNYL IN PSYCHIATRIC ILLNESS

By

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MANY chemical substances have been used to assist psychotherapeutic treatment. Abreactive procedures, using either depressant substances like sodium amytal, or excitatory substances like methedrine, or sometimes a combination of these substances, are standard procedures though, in everyday psychiatric practice, their use is limited.

In addition to these procedures, others have more recently been used. Busch and Johnson (1950) reported the use of LSD in eight patients with a psychoneurotic illness and Sandison *et al.* (1954) investigated the therapeutic value of this substance, emphasizing its value in obsessional disorders.

The search for an effective intravenous anaesthetic agent led to the synthesis of a series of cyclo-hexylamine derivatives. The first of these to be investigated clinically was 1-aryl-cyclohexylamine (Sernyl) It was found, however, that psychological disturbances limited the use of this compound in anaesthetic practice, but the investigation of these by psychiatrists has led to a number of interesting reports which have been reviewed elsewhere (Davies and Beach, 1960). Abreactions were reported by the anaesthetists (Greifenstein *et al.*, 1958) while its schizophrenomimetic properties were described by Luby *et al.* (1959). These publications suggested that Sernyl might be useful as an abreactive agent or, perhaps, like LSD, of value in more chronic conditions.

The aim of this paper is to report 60 interviews after I.V. Sernyl in five patients, and to suggest from this, possible uses for this drug.

MATERIAL

The five patients who received this treatment were in-patients at The Bethlem Royal Hospital under the care of Dr. Linford Rees. Some clinical information about them is shown in Table I, and a brief case history of each patient is given below:

TABLE I

Case No.	Sex	Age		Length of Illness	Number of Interviews with Sernyl
1	F	31	Personality disorder. Mixed neurotic picture	3 years	12
2	F	34	Affective disorder	6 years	9
3	F	33	Obsessional disorder	12 years	16
4	F	21	Anorexia nervosa. Obsessional personality ..	9 months	15
5	M	40	Obsessional disorder	10 years	8

METHOD

After a full psychiatric history had been obtained, patients were seen for three-hourly psychotherapeutic sessions each week. When treatment with Sernyl was decided upon, the patient was first given sodium amytal I.V. on two or three occasions, in order that she should become used to drug-assisted psychotherapy. Sernyl was then given twice a week by I.V. injections. The treatment was given in the patient's room, with the patient lying down. One mg. was given at first, and the dose was increased by 0.5 mg. on each succeeding occasion to a maximum of 5.0 mg. Optimum dosage seemed to be 3.5-4.5 mg. given over 3-5 minutes. In one patient (Case No. 2) Sernyl followed a number of methedrine injections and patient No. 5 had previously received 14 treatments with LSD. During the session the doctor played a passive role, recording all that was said or done, but neither suggesting topics of conversation nor encouraging those started by the patient. Afterwards, the patients were closely observed by the nursing staff. In the evening of the treatment day, the patients were asked to write down their experiences under the drug and, later in the week, these reports were discussed with the patients in a normal psychotherapeutic setting.

OBSERVATIONS

While a particular feature—e.g. restlessness or changes in bodily sensations or an abreaction—may be the main feature of a particular Sernyl experience, the following gives a general picture of the course of events:

The drug acts immediately and while the injection is being given, the patient often says that he is "beginning to go under" and may compare the sensation to being anaesthetized or of being drunk or of falling asleep. Often background noises are commented on by the patient as appearing to get louder. There is a feeling of incipient vertigo that is often made more severe by sudden movements, and the patient generally finds it more comfortable to lie still. Generally at this stage nystagmus is easily observed.

Feelings of numbness are complained of, particularly about the face and hands—"My hands feel different", "My lips are numb", "It's like having a tooth out under a local anaesthetic" are frequent remarks. At this time pin pricks are not felt as sharp. In addition, more pronounced feelings of bodily change sometimes occur to a marked degree. Sometimes it is that the hands seem huge or tiny, sometimes the legs seem a long way away and occasionally there are complaints that the whole body feels large at one moment and tiny at another—"I'm like Alice in Wonderland" one patient reported.

The patient's mood is not constant, but is generally one of euphoria. Marked emotional abreactions, however, occurred in each patient on one or two occasions, as significant episodes were remembered. On these occasions restlessness was marked but this did not cause concern. Emotional feelings towards the therapist are frequently expressed in unambiguous terms. The patient talks readily throughout the experience but repetition of words, phrases and sentences are particularly common.

No hallucinations occur at this dosage, but hypnagogic-like experiences are not uncommon.

The patient never loses touch with his surroundings and is always correctly orientated and responds correctly to stimuli, yet it is a marked feature of the experience that it is not remembered clearly afterwards. All patients underestimated the time of the experience, generally saying that it lasted 10-20

minutes when, in fact, it was two to three times this. After 30–45 minutes the patient will often say, “I am back to normal now”, then, after a return of symptoms, he will repeat this a few minutes later. Generally the acute symptoms subside after 45–60 minutes, though the patient may remain somewhat dazed and unwilling to move from the bed for another 30 minutes. Vomiting did not occur in these patients. Thereafter, for several hours, there may be a change in behaviour—sometimes described by the patient as being “pleasantly drunk”. It was noticeable that the three patients with obsessional symptoms lost some of these during these few hours. Occasionally thereafter the patient felt a little unwell for the rest of the day.

After 3 mg. of Sernyl one patient said, “Everything is getting bigger, bigger, bigger; I’m frightened, frightened, frightened—it’s a terrible feeling; I feel like a puppet with someone pulling the strings, strings”. Another said, “What on earth is happening to me—I don’t know—I am of different sizes, big and small, big and small. Space does not mean a thing, big and small, it’s delicious”.

Examples are given in the case reports of the patients’ reported experiences but the following contains many features that often occurred.

“After a few minutes, I seemed to develop a feeling of being away from the world and entered into a world of spiritual perfection. The view from my bedroom window took on a great significance with a profound impression of peace, distance and detail. Then the fear of blindness welled up inside me, bringing with it awful fear and panic. For years this fear of blindness has haunted me, particularly before dropping off to sleep—but not during the day. Then, quite suddenly, I returned to near reality with the view reverting to an ordinary pleasant one without detail or the feeling of ‘spiritual’. I noticed that I seemed detached from my body—my feet and lower part of the legs felt like blocks of concrete fixed to the ground. Life re-entered the body from the head downwards, finally connecting up at the solid part of my legs. For the rest of the session I had the feeling of alcohol wearing off. Throughout the evening I felt calmer than usual though I had a slight headache.”

OUTCOME OF TREATMENT

All the patients were discharged from hospital in a better state than that on admission. It is not possible to claim that this improvement was, in any major way, due to the Sernyl experiences because this treatment was but a part of the total therapeutic regime. One obsessional patient, though obtaining relief from her obsessions on the day of the Sernyl treatment, became increasingly depressed and received electro-convulsive therapy. It was not, however, thought that this was necessarily due to the Sernyl treatment. The other obsessional patients both believed that they had derived benefit from the treatment, while the other two patients appeared to be helped by the abreactions that occurred. It was expected that with this type of intensive treatment, difficult transference problems would arise, and these did, in fact, occur with two patients.

DISCUSSION

Only the possible therapeutic use of this drug will be considered here, as its action and comparison with other drugs had been mentioned in the previous paper.

In these five patients, Sernyl proved to be an effective abreactive agent,

marked abreactions occurring in each patient as significant episodes in their lives were remembered. This reaction was more marked and more effective than with sodium amytal (that all patients had received) and methedrine (that two had received). It seems likely that the changes in bodily sensations that occur may contribute significantly in assisting this abreaction. These patients all had long-standing illnesses but the results suggest that Sernyl might be evaluated as an abreactive agent in more acute conditions that have been precipitated by some catastrophe.

Perhaps more interesting are the results obtained in the obsessional patients, patient 5's history being particularly interesting in this respect. The transitory relief of obsessions after the experience is unlike that of LSD which often makes these patients worse for a time (Sandison *et al.*, 1954). This appears to be a profitable line for further investigation.

Oral Sernyl was only available towards the end of the investigation but preliminary results suggest that side-effects—e.g. dizziness and ataxia—may make dosage difficult to adjust. A few reports are available in the American literature about the use of oral Sernyl. Bodi *et al.* (1959) treated 32 patients with "psychosomatic disorders" with oral Sernyl. They found that it appeared to be effective in mild to moderately severe anxiety states, though side-effects were common. 1.5–3 mg. a day seemed the optimum dosage.

As has been mentioned, a common symptom of Sernyl administration is numbness of the face. Meyer *et al.* (1959) have used it to treat patients with facial pains occurring in various neurological syndromes; however, a third of the patients developed undesirable psychological symptoms of the type described.

CASE HISTORIES

1. An attractive 31-year-old woman was admitted to hospital complaining of depression, anxiety and restlessness. Her father had been a violent-tempered seaman who committed suicide at the age of 40 when the patient was 10. After this, his widow became increasingly irritable and unsympathetic towards her children. Our patient was the third of five children, only one of whom appears to be free of psychopathic traits.

In early childhood the patient was enuretic and frequently would wander away from home for many hours. She did well at school, however, and was a popular companion. On leaving school she worked in a baker's shop, but became bored and left. By the time she was admitted to hospital she had had forty-three different employments, but she had completed three years' nursing training and had worked in several hospitals on the continent.

At the age of 12, she was sexually assaulted and since the age of 18 had a series of intimate love affairs with several men. She was a sociable, outgoing and energetic woman, but was subject to unpredictable mood swings and there were obsessive traits in her personality make-up.

In 1955 she became irritable and depressed and received treatment from her general practitioner for nine months. In 1956, the symptoms returned with increased severity and she received out-patient psychiatric treatment. Despite this, attacks of anxiety and depression occurred, often with no apparent precipitating cause.

Two months before admission, after a quarrel with her fiancé, she broke off the engagement and, soon after this, her attacks of anxiety became more frequent and more severe.

Progress and Treatment. Initial psychiatric interviews were not productive, the patient denying her many personal problems. Sodium amytal interviews made her more relaxed but there was no affectively charged talk. A course of Sernyl was then given, twelve treatments being given in all. 1 mg. was given at first and this produced "a pleasant feeling—but I'm not quite real". At the next session she felt relaxed at first but then abreacted violently as she talked about her fiancé. Throughout the remaining sessions she talked easily but with marked emotion about her disturbed childhood and her series of love affairs. These abreactions occurred after disturbances in bodily sensations—"The reaction is rapid—I feel to be of different sizes—big and small, big and small—space does not mean a thing—it's delicious—the fingers of my left hand have become like pin-points and then the tiny, huge sensation comes over me in waves—I remember feeling like that when I was ill at about 7 years of age".

She was discharged from hospital five months after admission. Her symptoms had improved, but no basic personality modification had occurred.

2. A 34-year-old woman was admitted to hospital with symptoms associated with a chronic mild depressive illness.

Her parents' married life had not been happy, there had been many quarrels and the father, a friendly, tolerant man, finally left his wife in 1953. Her mother had always been "difficult and temperamental" and she had made four suicidal attempts before finally being successful in 1956. The patient is the eldest of four children and is the only one who has had psychiatric treatment.

Our patient developed normally and she did well at school until the parental quarrels increased in frequency and severity, when her school record deteriorated sharply. When she was nineteen she was invalidated out of the A.T.S. on psychiatric grounds and thereafter took a series of jobs until she married in 1946. This, however, was not a success and after a year she separated from her husband and was later divorced. As a person she was sociable but liable to minor mood swings and was never able to make decisions easily. She was sexually cold and complained, in fact, of "having shallow emotions".

Her present symptoms began in 1953 when her parents separated. "I tried to shut her problems out of my mind but I felt I was running away from my mother—I felt very guilty." Depression and indecision became more prominent after her mother's death and she also developed symptoms of depersonalization. Her work deteriorated and she said, "I had no incentive to live, yet I was afraid to take my life."

Treatment and Progress. After a month of twice weekly interviews, during which little affectively charged material was obtained, she seemed more depressed. Over a period of six weeks a weekly interview with methedrine was given. During this time she was, for the first time, able to talk about her feelings for her mother. Then she received nine injections of Sernyl over a five-week period. During these interviews she became very restless and there was much emotionally charged talk about her mother—this generally was concerned with her guilt feelings—"I killed my mother, I killed her, I killed her, I hate myself, I hate myself, I hate myself, I'm so wicked, wicked." Echolalia was quite marked in these interviews (unlike the Methedrine ones) as this example shows. In addition disturbances of bodily sensations occurred—"I feel to be floating, unreal, and my body feels different." After such an interview she wrote, "I feel relaxed and can't remember very well what I said and what I did."

On one occasion, unknown to the patient, Methedrine was given in place of Sernyl—"It's not the same today, is it? Usually I feel I want to throw myself about, but I don't now—I do not feel as funny as I usually do".

The clinical impression was that the patient derived benefit from the course of treatment. She left hospital after a five-month stay, having obtained new employment for herself.

3. A Maltese woman of 33 years was admitted to hospital for the treatment of a severe obsessional neurosis of some 12 years standing. Her father had died at the age of 60 of neurosyphilis; he was described as a strict, intolerant man. The mother is alive and well. The patient has a twin brother and together they are the youngest of seven children. Nothing definite is known about these siblings as they are in Malta, but all are described by the patient as being "highly strung and all make mountains out of molehills". They came from a middle-class home and there was a good standard of living. Her childhood appeared normal and there is no evidence of any neurotic traits. She was an average scholar and on leaving school, became a seamstress.

She first met her husband when he was serving in the Army and was stationed in Malta. They married seven years later but sexual relations were never satisfactory. There are two children, aged nine and four. Her personality is described as gay, happy, friendly but always over-particular about cleanliness.

Present Illness. For twelve years prior to admission she had become increasingly concerned with cleanliness. She would not allow any of the family to touch her things and if any of them touched her, she would have to wash herself. Gradually her activities became more and more limited and she would not touch things. She burnt many sets of clothes as she was unable to wash them. Compulsive hand-washing became more and more frequent and the condition of her home became filthy as she was finally unable to do any cleaning. On examination she was a small, undernourished woman, she was dirty and her teeth and hair were badly neglected. She washed her hands after touching anything, she was fairly cheerful on admission but was fearful of eating and washing in the communal atmosphere.

Treatment and Progress. She was treated with two injections per week of Sernyl, after initial sodium amylal interviews. During the interviews (sixteen in all) changes in bodily sensations were prominent. She talked much more freely and restlessness and echolalia were prominent. Prominent, too, was the fact that after every injection, for periods varying from 1-3 hours, there was a definite diminution in the obsessions. She would eat in company and wash from the communal basin. This relief was not obtained with intravenous sodium amylal. She abreacted many emotionally charged childhood episodes and sexually charged adolescent ones. A transitory feeling she described as, "I feel I am dying" occurred on nearly each occasion. Throughout the course of treatment she became gradually more depressed, but the relief of the obsessions that occurred after the injections suggested that oral Sernyl might help. However, with even a small dose (2.5 mg.) she complained of dizziness and after a few days this had to be discontinued. A course of E.C.T. helped her depressive symptoms and the patient was finally discharged having derived some benefit from her stay in hospital.

4. A 21-year-old nursing student, was admitted to hospital for the treatment of anorexia nervosa of nine months' standing. Prominent in the story were the marked obsessional traits in the personality make-up. Her father, a salesman, is alive, aged 47; he is a bad-tempered man who, for many years, has been frequently drunk. When the patient was thirteen, her mother left home and has not been heard of since. Prior to this there had been many parental quarrels, generally precipitated by the excessive drinking of both parties. When the patient was seventeen, her father remarried and the onset of the anorexia coincided with her stepmother's first pregnancy.

The patient's early childhood was marred by parental quarrels, but she did well at school, where she stayed until she was sixteen. She then took up office work until she began her nursing training at the age of nineteen.

Until her illness her periods had been normal. There had been no sexual experiences and sexual phantasies were denied. In 1955 she was thrown from a horse, was concussed and thereafter developed an illness characterized by anxiety, depressive and hysterical features, which was treated with E.C.T. Obsessional traits were prominent in her personality make-up, as were her difficulties in making friendships with men. Her illness began nine months before admission, when she started to diet and then rapidly lost weight. Amenorrhoea developed and weight loss continued until she had lost 3 stones in weight by the time she was admitted. She was seen on three occasions a week for psychotherapy. However, little emotionally charged material was obtained, her obsessional defences seemed to prevent any progress. On admission she was depressed and later, in association with a marked mood swing, she commenced to eat more and put on weight. She was discharged after two months in hospital, but was re-admitted two months later with a return of the symptoms. On this occasion, in addition to general management of the feeding problem, interviews under Sernyl were given, 2-3 per week.

She talked much more freely under the drug. Restlessness, sensations of bodily change and echolalia were marked. So, too, was a feeling of calmness and euphoria that persisted for 1-4 hours after the injection. Immediately after the injection there were no feeding difficulties. Prior to treatment with Sernyl, she felt that after eating she must walk rapidly round the garden half-a-dozen times. She was quite unable to prevent herself doing this, though she recognized its uselessness as a means of weight reduction. During the course of treatment, this particular symptom completely disappeared. There were marked abreactions about her parents—notably her mother, who had suddenly disappeared from her life. The desire to be "young, thin and a child" was frequently expressed as was her desire for food and the guilt feelings when she did eat.

As has been said, after the injection, she generally felt quite different; she wrote, "I felt like a child at supper, then I felt like skipping and dancing; I gave in to this feeling and felt so happy, I felt so light and wanted my food; I felt all the nurses were fond of me because I was a child. Later I became myself again and I realized I just can't be a child."

After sixteen treatments it was felt that psychotherapy without the drug was possible, and this is being continued with a gradual improvement in the patient's general condition.

5. A bachelor of 40 years was admitted to hospital because of an obsessional neurosis of ten years' standing. He is an only child and his parents are both alive and well. There is evidence in the mother of a marked obsessional personality. The family background was stable and financially secure. There is no history of neurotic traits in childhood. He stayed at school until he was 14 and was a less than average scholar. On leaving school he took up an office job and thereafter had a succession of jobs. He generally left, either because of his inefficiency or because he disliked the job. For three years prior to admission he had worked as a Post Office sorter. There appears to have been little sexual activity until he was in the late twenties, when he started to masturbate, always accompanied by sadistic phantasies—generally torturing women. He has always been a lonely man with no close friends, and is particularly shy of women.

His illness began about ten years previously—he started to arrange and re-arrange things in his rooms, he had to post letters without them touching the letterbox and to read the newspapers in a set order. Gradually the compulsions became more severe until, prior to admission, he was continually late for work because of his rituals in dressing and tidying his room. In 1955, he had nine months of psycho-analytic treatment which he terminated himself. On admission he was of asthenic build and was co-operative and of average intelligence. He talked well, with a knowledge of psychological terms, and was well aware of the intractable nature of long-standing obsessional illness.

Treatment and Progress. Treatment was commenced with LSD, given intravenously. He received fourteen injections of LSD with an increasing amount on each occasion—reaching 700 μ g. Little reaction occurred at the initial interviews but later interviews took on a very similar form which can best be summarized by his own description—"Following the injection, a rather unpleasant sensation came in—it was a combination of physical and mental discomfort. There was a nightmare world of blood and horror and horrible mental images of bodies with open wounds, bleeding, cut about, images of closed feminine eyes isolated from their bodies. All these images seemed to have movement—there was a kaleidoscope of bleeding bodies."

In addition, there were sexual phantasies about his mother and accounts from the many books on sadism that he had read. Then, unknown to the patient, 4 mg. of Sernyl was given

I.V. His talk was noted down—"It has worked rapidly today. Are you a doctor—am I insane—am I insane—am I dead—am I a sadist—am I a terrible sadist—why am I a sadist—am I talking—am I talking—blood, horror, torture—am I a sexual pervert—am I a sadist—killing and blood—torture, horror, death, killing—I am a murderer, I am Jack the Ripper—I want to wallow in blood—I want to love little girls, love little girls, love little girls. I am a sadist. I want to kill, destroy, slash, kill—am I a sadist?"

This kind of talk persisted for an hour, then he said, "I seem to have done a lot of incoherent talking. I don't seem to have had any horrible images. I just feel as if I have done a lot of silly talking—I seem to have lost contact with reality." Later he wrote about this first Sernyl experience—"I cannot remember much but it was not such an unpleasant experience as previously. There was no sense of physical and mental torment and no horrific mental images. I seemed to pass rapidly into a sort of state of delirium though I don't suppose this is the correct word. I appeared to lose touch with reality and seemed to spend much time in incoherent babbling of silly, obscene things. I seemed to be in another world, but I am afraid that the memory of the session is rather vague, hazy and not at all vivid as on previous occasions."

Thereafter he received 7 further injections of Sernyl and similar happenings occurred. The repetition of sentences and the subsequent poor recollection of the session being the main points.

The LSD experiences were extremely unpleasant ones for him, while the effect of Sernyl was not unpleasant; while the main effects of Sernyl passed off within 1-1½ hours, again, as in the two previous patients, there was a definite diminution of obsessional rituals for up to three hours afterwards. After LSD, however, he writes, "There is a desire to act in a compulsive way and there seems to be an increase in compulsive behaviour—it seems to be stepped up by the drug." This contrast between the drugs was interesting.

Throughout his three month stay in hospital he gradually improved and on discharge, he felt himself considerably improved to his state on admission.

SUMMARY

Five patients, suffering from long-standing psychoneurotic illnesses, received 60 treatments with I.V. Sernyl. The method of using the drug, and the drug experiences, are described and its possible value as a therapeutic agent discussed. Sernyl may prove to be valuable as a potent abreactive agent. Investigation into its use in obsessional states is also suggested.

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THE EFFECT OF STILBOESTROL IN TWO CASES OF MALE TRANSVESTISM

By

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THE possibilities of therapy in cases of male transvestism are very limited. There are a few references in the literature to the use of synthetic oestrogens and in these papers the aim has been to feminize the patient by hormonal castration. Benjamin (1) recommends the use of oestrogens for milder cases and Hamburger (2) has used them prior to surgical castration.

In the first case to be described stilboestrol was given to reduce libido on the grounds that the transvestist episodes were associated with overt sexual excitement and might thereby be reduced. In the second case it was used to relieve tension associated with the patient's unsatisfied desire for a male sexual partner. Oestrogens have often been used similarly in cases of homosexuality especially pederasty.

Case 1

This man is 47 years of age, a semi-skilled factory worker who has been partially deaf since infancy as a consequence of middle ear disease. He found school very trying because of this deafness. He was the 7th of 8 children of a carpenter and there was no family history of psychiatric disorder. His work record is stable as he has been at his present job since the age of 18. Outside his work he has well-developed interests. At 25 he married and now has three children (aged 20, 16 and 11). Coitus with his wife was always satisfactory until 18 months before his referral when she (also *aet* 47) showed loss of libido because of menorrhagia and would not have further relations. She would not attend the clinic and could not be brought into the patient's therapy.

He has had fantasies of living "away somewhere" where he could wear female clothes the whole time since his teens. He denies homosexual attractions and "doesn't understand homosexuals at all". Since his early twenties he has in private donned female underclothing, become sexually excited and masturbated. When referred to one of the St. Andrew's Hospital Out-patient Psychiatric Clinics in December, 1958 he was changing to female clothes and masturbating at least twice weekly and was desperately afraid of going on the streets in women's clothes and being prosecuted.

At interview he was a straightforward person of average intelligence clinically, who was tense and anxious about his condition. There were no physical abnormalities apart from his partial deafness, his body build and gait was masculine, and his genitals were normally developed.

He was prescribed stilboestrol 1 mg. b.d., having had the implications of this therapy fully explained. When seen a month later he had experienced relief with some depression and recurrence of the urge to cross dress in the last week. Dosage was increased to 1 mg. t.d.s. with complete suppression and after 3 weeks it was reduced to a maintenance level of 1 mg. per day. Six months later further reduction to 1 mg. per day for 5 days per week only proved inadequate after a month, and daily dosage had to be resumed. While on therapy (now 10 months) he has felt happier, free from tension and able to enjoy and develop his main interest running a small poultry farm. There has been no increase in breast tissue but softening of the testes. The urinary 17-ketosteroids were not studied.

Case 2

This man is 32 years of age and has no relevant medical history. There is no known family history of psychiatric illness, his father was a carpenter and died of pneumonia when the patient was 11. He has two sisters and one brother all of whom are older and in good health.

He has a constant pre-occupation with the feeling that he is a woman and requests surgical removal of his male genitals. He claims that this feeling was present at pre-school

age and that he was always aware of it throughout his school days. At 14 he was apprenticed to a carpenter but stayed only a few weeks subsequently being apprenticed to a tailor. He worked 4 years until his difficulties, especially jeers at his femininity, precipitated a depressive illness necessitating 8 weeks treatment in a mental hospital. Since that time he has done no work but lives at home with his elderly mother. He has no interests but does most of the housework. There are strong homosexual feelings but he admits only one very short-lived liaison with a man. He seems incapable of handling his homosexual urges and finds advances from other men distasteful. He would like always to wear complete female attire, but wears only a blouse-like shirt and some make-up, not daring to go any further for fear of arrest.

He has attended one of the St. Andrew's Hospital psychiatric clinics since March, 1954, but attendances have been irregular. He is of masculine build with normally developed male genitals, but adopts a feminine gait. His manner is withdrawn and resentful. In April, 1955 he was more than usually disturbed by homosexual urges and an attempt was made to inhibit them by prescribing stilboestrol 1 mg. t.d.s. and the patient obtained some relief. This medication was continued for 10 months by his family doctor. In May, 1957 it was resumed and as he attended the clinic irregularly medication was ordered by his general practitioner. In October, 1957 he was taking 10 mg. per day and in November, 1958, 12 mg. per day. When seen in August, 1959 he was taking 10 5 mg. tablets per day. He felt they feminized him and enabled him to attain his object by making his voice more feminine and his hair longer. He passively accepted reduction in dosage which was arranged through his family doctor but was disappointed that this was considered necessary.

DISCUSSION

The transvestism shown by Case 1 was of the auto-mono-sexual type described in Lukianowicz's recent review (3) and it would seem worth while trying oestrogens in this type of transvestism when symptomatic control is needed.

The patient described in Case 2 is a transsexualist. He derived little relief from the tablets and obtained large doses in an effort to attain femininity. There would seem little scope for oestrogens in transsexualists as they are not content with a limited symptomatic relief and from the evidence of this one patient may seek the unattainable goal of a sex change by higher doses.

SUMMARY

Two cases of transvestism are described both of whom received stilboestrol. Case 1 was of the auto-mono-sexual type and obtained great relief. Case 2 was a transsexualist and obtained excessive dosages in an effort to attain femininity.

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GENERAL PARESIS OF THE INSANE IN PEKING BETWEEN 1933 AND 1943

By

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INTRODUCTION

ALTHOUGH some years have passed since the end of the period under consideration, the subject matter is not altogether inappropriate. Neurosyphilis is now rare, though by no means completely abolished in the Western countries, and it is necessary to bear it in mind, for long-forgotten and undiagnosed cases are still liable to confront busy practitioners or specialists. In many parts of the world the situation is different and neurosyphilis is still frequently seen. Its global incidence may be waning but it is not yet a historical curiosity.

The present work was to be a complete analysis of 134 cases of general paresis of the insane (G.P.I.) admitted to the Peking Municipal Psychopathic Hospital between 1933 and 1943. As mentioned in our previous paper, Chu and Liu (1960), G.P.I. accounted for 7·3 per cent., after schizophrenia and manic depressive psychosis, ranking third in order of frequency. Its clinical manifestations, the main types of treatment and the remission rate of a 3-year follow-up period are especially considered. This study had to be completed in a very short time and certain information was unobtainable. Publication in the *Chinese Medical Journal* had been intended, but circumstances made this impossible and it is now offered in the belief that it will form a useful comparison in the evolution of the modern advances of the subject.

PRESENTATION

Of the 1,716 consecutive admissions to the Peking Municipal Psychopathic Hospital during the 10-year period 1933–1943, 134 were diagnosed as having general paresis of the insane. Of these, 109 were males, giving a male-female ratio of 4·4:1. The age range was from 20 to 73 years, the mean being 44. Nine were unmarried.

Table I shows the various provinces from which the patients originated.

TABLE I
Various Provinces Where the Patients Originated

	No. of Patients	Percentage
North China (Ho-peï=67 or 50 per cent.)	83	62·0
Peking	18	13·4
South China	16	11·9
Manchuria	13	9·7
Mongolia	1	0·8
Others	3	2·2
Total	134	100·0

The occupation and, therefore, the social status of these patients are indicated in Table II. It is interesting to note that they form an atypical group of

TABLE II
Classification of Occupations

	No. of Patients	Per- centage
Business men	27	20.1
Labourers, rickshaw pullers, domestic servants, cooks	22	16.4
Government officials, lawyers, telegram and post office workers	17	12.8
Policemen	14	10.5
Military and army men	11	8.3
Tailors, carpenters, Blacksmiths, chauffeurs } semi-skilled group	6	4.5
Prostitutes	3	2.2
Peasants	2	1.4
From poor house	2	1.4
No occupation	2	1.4
Student	1	0.7
Housewives	22	16.4
Not recorded	5	3.6
Total	134	99.7

Chinese, the great bulk of whom had the serene, non-migratory pattern of life of a peasant community. Wechsler (1947) pointed out that civilization and urbanization are accompanied by a greater liability to the contraction of venereal diseases. My own personal observations in China were that people without steady jobs, settled permanent homes and happy marital lives were much more prone to venereal diseases than those whose daily lives and environment were more stable, for instance, among the 22 housewives with G.P.I., only one patient, whose husband was a peasant, while 21 had husbands whose occupations were constantly changing. Financially, people of these types were better off with their ready-money wages and their better chances of making new social contacts. On the other hand, the peasants, though not financially inferior, had more limited opportunities for loose living, because their wealth was in a less fluid form and thus they had little ready money to spend; also the vast distances from country to town and communication difficulties impeded their chances. Further, the old traditional teachings, moral and family codes, respect and civility were still preserved in the rural areas, and a victim of any form of venereal disease would certainly be regarded as a disgrace and as a person lacking in regard to ancestral ethics.

CLINICAL HISTORY

The majority of the present series had advanced G.P.I. with severe psychosis and mental deterioration. Details of primary infection, its duration and treatment were therefore not readily obtainable. In 51 cases however, the incubation period between primary infection and the manifestation of G.P.I. was recorded, and ranged from one to thirty-nine years, the mean being 18.2 years. Eighteen cases out of the total of 134 received antisymphilitic treatment at the time of the primary infection. Another three received Chinese herb drugs (details not known), while the majority of the series had no antisymphilitic treatment before the development of psychosis and other clinical manifestations of G.P.I. In 118 cases, the period between the recognition of the first manifestation of G.P.I. to the time of admission was mentioned, the shortest being one week and the longest 5 years. The mean was one year one month, while in those with the dementing form, the period was much longer, being 1 year

9 months. During this period they were chiefly cared for by their relatives at home. Their unreasonable and progressively more degraded behaviour and conduct and their various psychotic episodes were well tolerated. Even their loud yelling and screaming noises were seldom complained of by their next-door neighbours, since the usual high-walled courtyard of the Chinese house served for better seclusion and privacy. What is more, a readiness to complain is not as a rule a typical Chinese character. It has been the general opinion among the Chinese people that any kind of mental illness is evil and the result of misconduct, discontent and unhappiness in life, and a neglect on the part of the younger members of the family. The resulting sense of guilt of the younger generations would induce them to keep the patient at home in the hope that special effort and re-awakened filial piety would bring about a cure. As a result, the patient was often deprived of antisyphilitic treatment and an early chance of cure. However, in the present series, 68 cases were brought to the hospital by their relatives, most of these being in a critical state of general health, such as severe emaciation, due to refusal of food, current infections or severe neurological or other medical complications. Another 58 were sent in by the police, because of absconding from home and consequently getting lost or creating public disturbances and so forth. Six were transferred from other hospitals or other social agencies.

MODE OF PRESENTATION AND REASONS FOR HOSPITALIZATION

The necessity for hospitalization was largely due to progressing mental deterioration leading to personal negligence. There was consequently a high percentage of poor general health with malnutrition and severe emaciation complicated by secondary infection such as pulmonary tuberculosis and the dysenteries. Acute neurological catastrophes of various types were the reason for immediate admission to hospital in a number of cases, for instance, convulsions occurred in 10, hemiplegia in four, paraplegia in one and "fainting attacks" in two. Other neurological complications such as loss of sphincter control or a mental state such that tube feeding was essential were also problems demanding admission.

As the patients were already in the late stage of the illness with fully-developed psychosis and mental deterioration, subjective somatic complaints such as headache, visual disturbances were rare. Very few sensory changes and lightning pains were mentioned even in cases of taboparesis.

Of the 134 patients, two had juvenile paresis (one died in hospital and the other was discharged without follow-up), and 13 had taboparesis. As shown in Table III, 98 (83 per cent.) of the 118 cases had psychosis. Sixteen (12 per cent.)

TABLE III
Types and Frequencies of Psychosis in General Paresis

Types of Psychosis			No. of Patients	Percentage	Total No. of Patients	Percentage
Expansive type	..	..	38	39.0	98	83
Manic type	..	..	31	31.6		
Schizophrenic state	..	..	22	22.4		
Agitated state	..	..	5	5.0		
Depressed state	..	..	2	2.0		
Dementing form	..	..			20	17
Not recorded	..	..			16 (or 12%)	
Total	..	..		100.0	134	

of the total of 134 cases either had only mild personality changes, or information concerning the initial symptoms or the presenting pattern of the disease was lacking. A few of the patients had mixed psychosis.

Most authors included manic phenomena as part of the expansive variety of psychosis or otherwise not clearly stated. While Bunker and Kirby (1926) classified 53 per cent. of their 106 patients as simple dementing type, only 19 per cent. expansive and 17 per cent. manic. Grinker and Bucy (1949), Elliot, Hughes and Turner (1952) also mentioned these as different types and considered that the dementing form was more common. The latter stated that the psychotic features often mask the underlying progressive mental deterioration, which commences in the early stages of the disease and ends in complete dementia. Conversely, Wechsler (1947) thought that the expansive form was the most common type. In practice it is not always easy to differentiate between the expansive and manic types of psychosis, a difficulty previously appreciated by Bunker and Kirby. In this study, an attempt was made to separate the two types on the basis of the criteria of presence of delusions of grandeur, euphoria and complete lack of insight in the expansive type; and flight of ideas, liability to change of mood and over-activity in the manic. Thus in the present series about 70 per cent. belonged to the expansive and manic types. Only 20 (17 per cent.) cases showed frank dementia, which was considered as a more advanced stage of the disease rather than a separate clinical type. Pfister (1926) mentioned that the psychotic manifestations of neurosyphilis of the Chinese patients followed the same pattern as those seen in Germany. My personal impression is that Chinese people are more reserved as a race, and therefore unless there is a preponderance of the extroverts contracting syphilis and eventual G.P.I.; or the destructive nature of the disease itself is the chief factor producing the expansive type of symptoms, it appears that the conventional concept that the pre-existing traits of personality make-up is the sole cause influencing the resulting psychosis is untenable for the Chinese patients with G.P.I.

PHYSICAL FINDINGS

Apart from the poor general health, malnutrition and current infections, frank evidence of the primary or secondary infection of syphilis was often present, such as penile scars which were frequently observed, and enlarged epitrochlear glands which, though not specific, were added proofs of the disease. Aortic regurgitation occurred only in one patient. Abnormal neurological signs were observed in most cases and in only 13.4 per cent. (Table IV)

TABLE IV
Abnormal Neurological Manifestations

						No. of Patients	Percentage
Reflex abnormalities	..	..	..	..	..	35	30.0
Tremors	..	..	..	..	..	29	25.0
Slurring speech	..	..	..	..	..	28	24.1
Ataxia	..	..	..	..	..	13	11.2
Hemiplegia	..	..	..	..	..	4	3.4
Paraplegia	..	..	..	..	..	1	0.9
Deafness	..	..	..	..	..	1	0.9
Impaired sphincter control	..	..	..	..	..	5	4.3
Not recorded	..	..	..	..	..	18	
						(or 13.4%)	
Total	..	..	..	..	..	134	

were there either normal findings or a deficiency in the recorded information. The majority of the abnormal findings were exaggerated deep reflexes, such as knee jerks and ankle jerks, absence of the superficial reflexes and positive Babinski and Romberg signs. In five cases the knee and ankle jerks were diminished and in another seven, absent. Unfortunately, these latter patients had the additional complication of malnutrition and vitamin deficiency, especially of the B Group, and the diminished or absent reflexes may be related to this rather than to the neurosyphilis. Tremors of the facial muscles, tongue or extremities, slurring of speech and ataxia all occurred in decreasing order of frequency. Sensory changes including superficial, deep and vibratory sense loss were only recorded on a few occasions. This was largely due to the patients' mental state and the pressure of work of the medical staff during the war years, both of which contributed to the failure to record this information. Thus the result seems much lower than the 20-30 per cent. given by Grinker and Bucy (1949). Pupillary abnormalities are given in Table V.

TABLE V
Pupillary Abnormalities

	No. of Patients		Total No. of Patients	Per- centage
	Male	Female		
Argyll Robertson pupils ..	54	8	62	46·3
Irregular and fixed pupils ..	0	3	3	2·3
Optic atrophy	1	2	3	2·3
Normal findings	54	12	66	49·2
Total	109	25	134	100·1

Sixty-two patients (46·3 per cent.) presented with Argyll Robertson pupils on admission; in a further three, all women, the pupils were irregular, fixed and non-responsive to light or convergence. Two of the three gave a history suggesting G.P.I. of at least 4 years duration, while in the third, the duration of symptoms was not known. There were three cases of optic atrophy, of which two were of very mild form. Another four cases had blurred vision, but no evidence of optic atrophy was observed, although one had taboparesis.

LABORATORY INVESTIGATIONS AND DIAGNOSIS

The diagnosis was based mainly on clinical findings and confirmed by the laboratory investigations. Wassermann reaction (W.R.) on blood and cerebral spinal fluid were performed routinely before treatment, during intervals between courses of treatment and during the follow-up period. The anti-complementary (A.C.) results for C.S.F. in 6 (5·2 per cent.) cases shown in Table VI were possibly due to other parasitic infections or delayed transportation to the laboratory. Delivery had to be done under unfavourable and difficult conditions and contamination was not unlikely and thus explains the comparatively low percentage of positive W.R. of the C.S.F. The qualitative globulin tests were done by the Pandy and Nonne methods. Quantitative estimations of protein were not recorded. Lymphocyte counts were within the expected range for similar cases of G.P.I. Because of missing data in some of the recorded cases, these were excluded from calculation of the percentage.

TABLE VI
Laboratory Investigations

	No. of Patients	Per-centage
Blood:		
Positive W.R. with Paretic Lange curve	123	95.5
Negative W.R. with positive C.S.F., W.R. and Paretic Lange curve	6	4.5
Note missing or not recorded	5	
Total	134	
C.S.F.:		
Positive W.R.	105	92.2
Negative W.R. with positive blood W.R. and Paretic Lange curve	3	2.6
A.C. (4 of these with positive paretic curves)	6	5.2
Note missing or not recorded	20	
Total	134	
Lange colloidal gold test		
Paretic curve	112	98.2
Non-paretic curve	2	1.8
Note missing or not recorded	20	
Total	134	
Total protein and globulin		
Increased	63	92.7
Normal range	5	7.3
Note missing or not recorded	66	
Total	134	
No. of Cells (Lymphocytes) No. of Patients		
0- 9	80	Excluding missing cases
10- 45		
50-109		
110-199		
200-300+		
Note missing or not recorded	54	
Total	134	

TREATMENT

As seen in Table VII, a total of 93 patients received antisyphilitic treatment. Owing to poor general health, secondary infections or other complications,

TABLE VII
Treatment

	No. of Patients	Im-proved	Per cent.	Station-ary	Per cent.	Worse	Per cent.	Died	Per cent.	No Follow Up	Per cent.
Neoarsenical compounds	39	10	25			4	10	8	20	18	45
Arsenical compounds (Arsphenamine)	1										
Tryparsamide	45	21	47	10	22	3	14	3	20	5	11
T.A.B. vaccine	21	9	43			5	25	3	14	6	29
Malaria therapy	20	8	40					3	15	4	20
Relapsing fever therapy	3	2	67	1	33						
Bismuth and iodides	17										
Total No. of patients received treatment	93										

antisyphilitic treatment had often to be postponed. 13.4 per cent. of the patients discharged themselves before the full course of treatment had been completed. A further small number of patients were too ill to continue treatment and in others death occurred before treatment was commenced. The outstanding

limiting factors in treatment were the patients' lack of capacity for co-operation, and the high cost of drugs and of hospital treatment in general.

Combined and alternating schemes of antisyphilitic drugs and fever therapy were adopted for most of the patients. A course of treatment usually consisted of bismuth and arsenicals, and in certain cases iodides were also used. In the early years, trivalent arsenicals were mainly used, but in the latter part pentavalent arsenicals (tryparsamide) were employed more frequently. Between the courses of arsenicals, one of the forms of fever therapy was given. Some patients received two or three courses of treatment in a one-, two- or sometimes three-year period. Others for medical or financial reasons had fever therapy alone.

Of the 45 cases treated with pentavalent arsenicals (tryparsamide), 21 (47 per cent.) improved, 10 (22 per cent.) did not improve or became worse, 9 (20 per cent.) died and 5 (11 per cent.) discharged themselves against advice and thus no further information was recorded. Of the 40 patients treated with trivalent arsenicals, 10 (25 per cent.) improved, 4 (10 per cent.) got worse, 8 (20 per cent.) died and 18 (45 per cent.) discharged themselves. The improvement rate with tryparsamide therapy was obviously better than that with trivalent arsenicals, a finding which is universally agreed by all clinics and these figures are closely parallel with those of Solomon and Epstein (1936) who claimed 42 per cent. remissions. As in other clinics (Moore, 1947), we found that a better result was obtained by the use of tryparsamide following malarial therapy. In our experience, relapsing fever was a promising method of induced fever therapy, but unfortunately the spirochaeta recurrentis blood was not always readily available.

When fever was induced by T.A.B. vaccine, the standard technique and dosage was used. For instance, a small test dose was given initially, followed by a gradual increase in the amount, until the desired dose was reached. This was maintained for a minimum of 12 injections, given daily, every other day, or every few days according to the tolerance of the patient. Further adjustment of dose was regulated as necessary by the height and duration of the pyrexia required. Unfavourable side-effects were seldom encountered. There was, however, one patient, a man aged 44, who gave a history of contracting primary infection when he was 28 and having received an incomplete course of antisyphilitic treatment at the Peking Union Medical College Hospital. He was ill with general paresis for a year before admission. Diagnosis was confirmed by blood and C.S.F. investigations. He was treated with tryparsamide and T.A.B. vaccine and was doing well both clinically and serologically until the 9th injection of T.A.B. vaccine, in the second course of which he suddenly developed severe anaphylactic reactions and died quickly of acute pulmonary oedema. This was the only death attributed to treatment in the present series.

Tertian malarial blood was generally obtained from fellow patients for malarial therapy. Two-thirds of the cases treated with malarial therapy received 5 c.c. of blood subcutaneously immediately after withdrawal from a malarial patient. The incubation period for this method was of the order of two weeks or a little longer. Another one-third of the patients received 2 c.c. of the malarial blood intravenously. The incubation period of this method was 6-10 days. No untoward side-effects resulted from malarial therapy.

Comparison between treatment with T.A.B. vaccine and malaria is shown in Table VII and indicates that there was no difference between the two from the remission point of view, though Wagner von Jauregg (1922) reported better results with malaria in his pioneer work and this was found by many others.

The disadvantages of T.A.B. vaccine therapy were that, in our experience, it was more expensive and that the dosage had to be gradually stepped up and separate injections were required for each attack of pyrexia. However, once the trial dose and the subsequent adjusted dose were obtained, the numbers and heights of the pyrexias and the intervals between pyrexias could be regulated at will. On the other hand, in malarial therapy, the malarial blood could be obtained free, but it also had its drawbacks, especially when given by the subcutaneous route as the exact incubation period was not always certain, particularly in an endemic area where large percentages of patients have had previous infection and immunity was high. The classical pattern of clinical manifestations was often modified, and the long uncertain interval before the onset of pyrexia was often a cause of anxiety among the medical and nursing staff, as well as the relatives. Furthermore, it was our experience that the desired number of attacks of pyrexia was frequently not reached before the disease terminated itself and quinine or other anti-malarial drugs were seldom needed, and there was usually no rigor preceding the febrile phase. The reason for this is probably due to the immunity gained by previous infection, and thus some form of resistance was present and, as a result, two or three attempts of administration of the malarial blood were required before success. Other drawbacks included the frequent irregularity of the attacks and the failure to reach the desired degree and duration of pyrexia. On the other hand, because of this high resistance often met in the patients with chronic malaria, there was no death directly attributable to malarial therapy. In contrast to similar therapy in malarial free countries, high mortality rate was often mentioned, e.g. Nonne (1925) in Germany, Bunker and Kirby (1926) in America and many others.

FOLLOW-UP

Table VIII shows the follow-up figures after a three-year period for all cases except the last 10 who had either a shorter period or no follow-up at all. Of the 48 deaths, 29 occurred in hospital and 11 within 3 years of discharge,

TABLE VIII
Three Year Follow-up

	No. of Patients	Percentage
Recovered or complete clinical remissions ..	13	9.7
Improved	24	17.9
Stationary	12	9.0
Worse	3	2.2
Discharged—cannot be traced	13	9.7
Discharged against advice	18	13.4
Transferred to other hospital (P.U.M.C.) ..	3	2.2
Died	48	35.8
Total	134	99.9

eight died of intercurrent disease, three to five years after discharge. No worthwhile records of serological studies are available for statistical purposes during the follow-up period. Since most of the information available was obtained by home visits and questionnaires, only 10 per cent. of patients returned for checking of psychoneurological status, serological and C.S.F. examinations. The rate (10 per cent.) of complete clinical remissions in a three-year period is much lower than that (20 per cent.) given by Nicole and Fitzgerald (1934) in

their 10-year follow-up. The main reason for this may be that most of the present series were very advanced cases.

DISCUSSION

The percentage (7.3 per cent.) of G.P.I. represented at the Peking Municipal Psychopathic Hospital is not especially low when compared with Grinker and Bucy's (1949) 5-8 per cent., and Henderson and Gillespie (1950) summarized as 5-15 per cent. for the British mental hospitals. The present work does not support the statement by Lennox (1923) who found on proportion basis that syphilis was more common in China than in America and neurosyphilis comparatively rare. It seems the figures given at different periods before the antibiotics were much the same, for instance, the analysis by Furbuch (1924) which was approximately 10 per cent. It was only since the intensive use of antibiotic therapy that the figures had sharply declined. This was illustrated by the work of Bauer (1952), and the declined incidence of neurosyphilis in this country was well summarized by Purdon Martin (1956).

The bulk of the patients in the present series belonged to the urban population, only 1.4 per cent. coming from the rural community. The disease was often hopelessly advanced by the time of admission to hospital, due mainly to the special social and family traditions and customs that existed. Of the 29 that died in hospital, 23 occurred soon after admission or soon after the treatment started. In addition, there was the frequent difficulty or impossibility of raising sufficient money for expensive treatment and hospitalization, none of which could be obtained free for the majority of the patients. Only 18 patients (13.4 per cent.) received antisyphilitic treatment before the onset of neurosyphilis. Therefore in the majority, the pattern of the disease was unaltered by the advent of modern treatment. The incubation period and clinical manifestations of onset and development could be observed as in the original descriptions of the disease.

Following the original report of Wagner von Jauregg (1922), better clinical results from malarial therapy soon appeared from all clinics. Its value was not limited to therapeutic instances alone, such as Wilson (1928) and Greenfield (1929) after examining the brain tissue of patients who died following malarial therapy found that the spirochaetes had either disintegrated or disappeared. It was also effective as a prophylactic measure. O'Leary (1931), Moore (1947), Grinker *et al.* (1949) and many others based on their accumulative experience, emphasized its use in early and asymptomatic neurosyphilis to prevent late parenchymatous syphilis. However, other workers, Fraser and Duncan (1921) and Pfister (1926) deduced from their experience that treatment, especially at the stage of the development of natural resistance, might encourage the production of G.P.I., and suggested that the unbalanced process of establishing immunity resulted in the antisyphilitic therapy leading to the invasion of the parenchymatous tissue of the central nervous system by the spirochaetes. However, in the present series, only 13.4 per cent. received inadequate antisyphilitic treatment at early stages of the disease.

Experience in an endemic area suggests that repeated attacks of malaria stimulate body resistance and progressively increase immunity to malarial infection. Moore (1947) put forward the suggestion that malaria induces mesoblastic, but resists parenchymatous types of lesions. The work of Mingazzini (1927) illustrated that previous malarial infection did not prevent developing immunity and cure in induced malarial therapy. This possibly

explains the claims by Parsons (1928) and Dumolard, Aubrey and Sarrony (1930) of the absence or rarity of G.P.I. in Haiti Island (where mainly the pernicious strain of malaria was prevalent), or among the native Algerians. Peking is certainly not situated subtropically; however, it is very much an endemic malarial area (Meleney, Lee and Chung, 1927) and, according to the previous argument, the logical conclusion might be drawn that G.P.I. should be less prevalent there than in malaria-free areas. Conversely, Wu (1927) in his work on incidence of syphilis in various cities in China showed that his figures were closely correlated with that reported in Germany, Great Britain and U.S.A., and Wei (1927) found that the incidence of *tabes dorsalis*, being 4.6 per cent. among the syphilitic patients, was considered as not less common than in Europe and America. Unfortunately, no reliable statistical studies have been made of the relative incidence of neurosyphilis in those who had malaria before or after the primary syphilitic infection and those who did not. Mingazzini, limited to only 7 cases, led him to conclude that previous malarial infection did not prevent the development of G.P.I., nor did it alter the incubation period between the primary syphilitic infection and the onset of G.P.I. He was of the opinion that G.P.I. is no less common in endemic malarial areas than elsewhere. The incidence of G.P.I. among the population of the Peking Municipal Psychopathic Hospital was certainly comparable with that in Britain and America, and thus does not support the supposition that G.P.I. is less common than in malaria-free areas.

Another debatable point of interest is that in the present series, the rate of remissions in both the T.A.B. vaccine and malarial treated groups was the same. This is contrary to Wagner von Jauregg's original finding and to most other authorities favouring malarial therapy. Could the natural high immunity, both for malaria and typhoid fever, which existed in Peking among the majority of the patients, be postulated as one of the factors for this controversy? Within the limit of my observation, I am unable to give a satisfactory explanation.

SUMMARY

A summary of the present survey is as follows:

1. General Paresis of the Insane occurred in 7.3 per cent. of the inmates of Peking Municipal Psychopathic Hospital between 1933 and 1943, a figure which is similar to that in Britain and America. Age incidence averaged 44 years. Sex ratio of male : female = 4.4 : 1.
2. The dominant form of psychosis in the present series studied were expansive and manic types, consisting of 72 per cent.
3. 95.5 per cent. blood and 92.2 per cent. C.S.F. gave positive Wassermann reactions.
4. Equally effective results were obtained from both malarial and T.A.B. vaccine therapy. Significantly higher remission rate obtained from pentavalent than that of trivalent arsenicals.
5. Malaria was the cheapest form of fever therapy in Peking. No mortality occurred during or immediately following malarial therapy.
6. A 3-year follow-up period is reviewed and showed 10 per cent. of complete remissions, and 18 per cent. with clinical improvement. The high rate (36 per cent.) of death is probably due to the advanced state of the disease on admission.

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A CLINICAL TRIAL OF FOUR TRANQUILLIZING DRUGS

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IN the six years that have elapsed since the tranquillizing drugs have been introduced for the treatment of mental illness, psychiatrists have been overwhelmed by the multiplicity of drugs, each claimed by its manufacturer to be more effective and less toxic than all the others. Contemporaneously, there has been a demand for the better assessment of the value of therapy in psychiatry with less reliance on clinical impression and more on the controlled trial (Eysenck, 1957; Foulds, 1958). It is quite impossible for each clinician to familiarize himself with each new drug, and it is difficult to carry out a fully-controlled double-blind trial on more than a small proportion of them. Moore (1959) has suggested a centrally-controlled trial of the tranquillizing drugs in schizophrenia by a body such as the Medical Research Council (1954) similar to the study on aspirin and cortisone in rheumatoid arthritis. Difficulties concerning diagnosis, and, probably more important, variations in the environment of the treatment situation which are of so much importance in determining the outcome of a mental illness, militate against the successful pursuance of such a scheme, and do not appear to have been overcome so far.

It is generally recognized that chlorpromazine has established itself as a reliable drug, useful in the treatment of tense agitated patients, particularly schizophrenics and to a lesser extent agitated depressives. It does suffer from the disadvantage of producing some toxic reactions including jaundice (in about 2 per cent. or less of cases) and, much more rarely, blood dyscrasias. It is because of these disadvantages that a continued search for an equally effective but less toxic compound is justified, and provides the problem of assessing newer drugs to see if they are equally efficacious yet less toxic.

Using chlorpromazine treatment as a base line we have compared with it three newer tranquillizing drugs which are also phenothiazine derivatives, utilizing the dosage recommended by the manufacturers as equivalent to a therapeutic dose of chlorpromazine. In choosing patients for the trial, we have confined ourselves to the single indication that we would have regarded this particular patient as suitable for treatment with chlorpromazine before the advent of the alternative preparations. This meant that the patient showed a high degree of tension or agitation, usually due to a schizophrenic or agitated depressive illness, with an occasional obsessional neurosis manifesting severe tension.

The drugs included in the trial are:

1. Chlorpromazine ("Largactil"—May & Baker). This was the first of the phenothiazine compounds in general clinical use. It was developed in France and came into psychiatric use in this country in 1953. It has been reported as valuable in the treatment of a large number of conditions including schizophrenia, agitated depression, mania, alcoholic delirium and to a much lesser extent in the neurotic illnesses. It relieves the symptoms of agitation and tension, rather than curing any specific illness, though some workers believe it has a specific action in schizophrenia. The usual dosage is 150–300 mg. daily, though reports of high dosage of up to 2,000 mg. daily have appeared. Toxic effects include rashes, pyrexia, jaundice, agranulocytosis and Parkinsonism. Cost of one week's treatment in hospital at 150 mg. per day=3s. 9½d.

2. Promazine ("Sparine"—Wyeth). This is chemically very similar to chlorpromazine but lacking the chlorine atom. It is claimed that the injection is less painful, and more important, so far no cases of jaundice have been reported. Dosage is similar to that of chlorpromazine. Cost of one week's treatment in hospital at 150 mg. per day=3s. 10d.

3. Acetyl promazine ("Notensil"—Benger). In this drug the chlorine atom of chlorpromazine is replaced by an acetyl group. It is claimed that it is equally effective in half the dose, and no cases of jaundice or agranulocytosis have been reported. The effective dose is considered to be 75 mg. a day and the cost of one week's treatment in hospital is 2s. 0½d.

4. Methotrimeprazine ("Veractil"—May & Baker). This is a new phenothiazine compound, chemically related to chlorpromazine, with a methoxy radical in place of the chlorine, and a somewhat different side chain. It is available as the acid maleate instead of the hydrochloride. It is claimed to have the same central effects as chlorpromazine, including an anti-adrenaline effect, and also quite marked anti-histaminic action, similar to promethazine. French workers have found it to be as effective as chlorpromazine in the treatment of schizophrenia, and that a smaller dosage can be used. There are no reports of the more serious toxic reactions, such as jaundice or blood dyscrasias. Dosage is 120 mg. daily—no cost is as yet available.

METHOD

Patients were selected for this trial on the basis that they were considered suitable for treatment with one of the newer phenothiazine tranquillizing drugs. Once the doctor indicated that the patient was to take part in the trial the pharmacist, using a pre-arranged method of randomized allocation dispensed one of the four drugs in the appropriate dosage. This was based on a standard dose of chlorpromazine, and each patient was started on 25 mg. thrice daily for three days and then increased to 50 mg. thrice daily. The equivalent quantities of promazine, acetyl promazine and methotrimeprazine were, 25, 12.5 and 20 mg. increasing to 50, 25 and 40 mg. respectively. The doctor did not know which drug was being given, but all patients were receiving an active preparation, and once started on a particular drug, this was continued without change for the duration of the trial although the dose could be adjusted if thought advisable. The trial on any individual patient was continued until the doctor was satisfied that the patient was fit for discharge, or else that the drug was either totally ineffective, or that some additional treatment such as electroplexy was indicated. Since this was a purely clinical trial, superimposed

upon an ordinary treatment programme, no strict rules were adhered to as to the length of time a patient was on a particular drug, but a minimum of four weeks' treatment was allowed if the patient was considered as having participated in the trial. Any patient whose treatment was changed before the end of the 4th week was not assessed.

At the conclusion of the course of treatment for a particular patient, either on changing to another form of treatment or on discharge, his condition was assessed before the particular drug used was ascertained. Three degrees of effectiveness were recognized. The drug was rated as bringing about total recovery or at least contributing markedly to the clinical improvement, or secondly, as assisting in the treatment of the patient, possibly in combination with electroplexy, or lastly being ineffective. (Side-effects were also noted.) Scores of 2, 1 or 0 were given respectively.

RESULTS

Ninety-two patients were included in the trial, 40 male and 52 female. Ages ranged from 16 to 81 with a mean age of 47.1 years. The mean age in each of the 4 drug groups was comparable.

Diagnoses are shown in Table I, in which also is shown the number of patients receiving each drug.

TABLE I
Distribution of Patients According to Diagnosis and Sex

Diagnosis	Chlorpromazine		Promazine		Acetyl Promazine		Methotrimeprazine		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
Schizophrenia ..	9	5	8	2	7	4	4	4	43
Agitated depression ..	2	6	4	9	2	11	0	8	42
Other diagnoses ..	1	2	1	1	1	0	1	0	7
Total ..	12	13	13	12	10	15	5	12	92

Table II shows the number of patients achieving each of the ratings in the separate drug groups.

TABLE II
Number of Patients Achieving Each Rating

	Schizophrenia			Depression			Other Diagnoses		
	Much Im-proved (=2)	Helped (=1)	Nil (=0)						
Chlorpromazine ..	5	6	3	1	4	3	0	2	1
Promazine ..	3	4	3	2	5	6	0	0	2
Acetyl promazine	2	4	5	2	5	6	0	0	1
Methotrimeprazine	4	2	2	1	3	4	0	0	1

While no patients were assessed before the end of the fourth week, in practice patients received the drug for an average of 9 weeks.

Table III shows the average scores achieved by each group of patients.

TABLE III

Average Score on Each Drug

Drug	No. of Patients	Average Score of All Patients on Drug	Average Score for Each Diagnostic Group		
			Schizophrenia	Depression	Other Diagnoses
Chlorpromazine ..	25	0.96	1.14	0.75	0.67
Promazine ..	25	0.76	1.00	0.69	0
Acetyl promazine ..	25	0.72	0.82	0.69	0
Methotrimeprazine	17	0.94	1.4	0.75	0

By means of t-tests it was shown that there is no significant difference between the mean scores of each group of patients receiving the different drugs. Nevertheless inspection of the results shows a trend towards a higher score with chlorpromazine and methotrimeprazine.

Side-effects

No cases of jaundice developed during the series. Three patients were found to have falling white cell counts while receiving drugs, one having acetyl promazine and the other two methotrimeprazine. There were no symptoms in association with the granulopenia which returned to normal on stopping the drug concerned.

The white cell counts of two of these patients were as follows:

<i>Patient D.R.</i>					<i>On Methotrimeprazine</i>	
					<i>Total</i>	<i>Per cent. Polymorphs</i>
25 June	..	..	..	..	4,760	60
1 July	..	..	..	..	3,360	68
15 July (drug stopped)	..	..	..	..	2,720	58
17 July	..	..	..	..	3,320	59
19 July	..	..	..	..	3,840	70
22 July	..	..	..	..	4,560	70

<i>Patient V.R.</i>					<i>On Acetyl Promazine</i>	
					<i>Total</i>	<i>Per cent. Polymorphs</i>
2 January	..	..	..	..	3,920	
9 January	..	..	..	..	3,760	
16 January	..	..	..	..	5,520	
23 January (drug stopped)	..	..	..	..	3,280	58
25 January	..	..	..	..	4,680	66
27 January	..	..	..	..	4,600	60
29 January	..	..	..	..	4,240	65
31 January	..	..	..	..	5,040	66

There were no other disturbing side-effects such as Parkinsonism, rashes or pyrexia.

DISCUSSION

This study was planned, not as a purely research project but with the object of combining treatment and research, so that the clinical aim of pressing on with the treatment and at the same time achieving a contribution to the very pressing problem of evaluating some of the many new drugs which have been thrust into the lap of the psychiatrist. We are well aware of its defects and limitations. A more refined research technique involving prior periods of observation followed by placebo reactor elimination periods would have involved weeks of delay in starting it and also confused the effects of the drug action by making environmental influences play a more potent role. The ethical problems of delaying effective treatment and using inert preparations for purely scientific reasons were also eliminated. These aspects can be very important, as patients suffering from psychiatric disorders are less able to appreciate explanations of research procedure and be buoyed up by the uplift of making a personal contribution to scientific knowledge, than those suffering from the many medical and surgical disorders. If the distressed and paranoid patients feels he is being experimented upon (and the belief that something of this nature is going on can easily become apparent to more intelligent patients), he or she sometimes feels aggrieved and resentful. In a trial of this type, treatment then goes on expeditiously, all patients receive active preparations and standard conditions prevail. Some base line, or standard of comparison, is essential. If one has a drug with an established clinical effect, this may be taken as a base line with which to compare other drugs. It is our opinion that chlorpromazine has now achieved such recognition and may be used in this way.

The results show that each of these four drugs exerts a comparable effect, and if that of chlorpromazine is accepted as satisfactory in the control of tension and agitation, then the other three drugs must be accepted as giving equally satisfactory results on the basis of this trial. Further, inspection of Table II shows that each drug had approximately the same proportion of poor, moderate and good results in each diagnostic group. This bears out Sargent's contention (Sargent, 1956) that one must continue one's search until one finds the drug most satisfactory for each individual patient.

Inspection of Table III would appear to confirm the more recent views of other workers, that the phenothiazine drugs are much more effective in schizophrenia than in depression.

SUMMARY

A trial, designed chiefly to combine research and treatment, of four tranquillizing drugs was carried out on patients with symptoms of tension and agitation. Chlorpromazine is accepted as satisfactory in the treatment of such symptoms and the results with Promazine, Acetyl Promazine and Methotrimeprazine are compared with it.

No statistically significant difference is found between the four drugs.

ACKNOWLEDGMENTS

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A PROGNOSTIC STUDY OF NEUROTIC PREGNANT PATIENTS—PRELIMINARY COMMUNICATION

By

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THE Anglo-American literature relevant to psychiatry and obstetrics reveals studies of the puerperal psychoses (Tetlow, 1955); papers describing the psychological reactions experienced during pregnancy and labour (Tobin, 1957; Kartchner, 1950) and retrospective studies of patients presenting with obstetric abnormalities of pregnancy and labour (Coppin, 1958; Caldwell, 1958; Cramond, 1954). The present paper describes the psychiatric and obstetric follow-up of a group of neurotic pregnant women, a study of similar material not being previously recorded in the literature.

AIMS OF INVESTIGATION

A number of questions of psychiatric and obstetric interest were formulated and an answer sought in the available data. To achieve clarity, the psychiatric and obstetric aspects of the group have been separated, though it is appreciated that this is an artificial distinction when considering the total reaction of the individual patient. Answers were sought to the following questions: (1) do pregnant women with overt neurosis exhibit any greater incidence of obstetric abnormality and if so what are the abnormalities; (2) can the obstetrician be advised as to the expected behaviour in labour of his patient; (3) what may be the expected psychiatric reaction of a neurotic patient in whom pregnancy supervenes; (4) are there any psychiatric differences between the patients who are neurotically ill before becoming pregnant and those in whom the pregnancy immediately ante-dates their illness; (5) are there any psychiatric differences between patients whose pregnancy is "illicit", compared with those in whom it is legitimate; (6) what is the psychiatric prognosis of such patients.

METHOD

All patients of the Bethlem Royal and Maudsley Hospitals who were diagnostically classified as suffering with a neurotic illness and pregnancy were followed up by letter, to their hospital maternity unit or medical practitioner, seeking information on abnormalities of pregnancy and labour. Adequate data were obtained in 22 patients. The age range was 18 years to 38 years. One patient was under 20 years, 12 were between 20 years and 30 years and 9 were over 30 years. The patient under 20 years of age, 6 of the "20-30 years group" and 4 of the "over 30 years group" were primiparae, giving a percentage of 50. Of the multiparae, 4 were multipara 1, 1 was multipara 2 and 4 were multipara 3 or more. Of the 22 patients, 13 had legitimate and 9 had illicit conceptions. Illicit includes both illegitimacy and conceptions in married women resulting from intercourse with men other than their husbands. Of the illicit group, 5 were married and multiparous, 4 were unmarried and primiparous. Of the 13 legitimate pregnancies, 7 were primiparous, 6 were multiparous.

The Dulwich hospital maternity unit provided control data of greater specificity there than obtained from the Aberdeen maternity unit or King's College Hospital (Table I). From Dulwich Hospital a random selection was

TABLE I

Percentage Comparison of Obstetric Abnormalities in Total Neurotics with Control Groups

		Neurotic Group	Aberdeen	K.C.H. 1954	K.C.H. 1956	Dulwich Hospital
Total Nos.		22	5,702	784	858	92
<i>Pregnancy:</i>						
Essential hypertension	..	18.2	4.7	1.5	2.9	1.5
Pre-eclamptic toxæmia	..	4.5	3.8→19.3	10.0	9.3	11.3
Prolongation		9.1	10.0	—	—	3.2
<i>Labour:</i>						
Caesarean section		4.5	1.5	8.5	9.9	1.6
Use of	} primiparae	..	9.1	9.2	9.2	6.6
forceps		..	2.2	6.5	5.4	0.0
Prolongation		4.5	13.5	1.5	1.4	12.9
Disturbed behaviour	..	13.6	—	—	—	2.2

made of white patients including legitimate primiparae (30 patients), legitimate multiparae (32 patients) and illegitimate primiparae (30 patients) of the same age as the studied group. No control data was available for married women with illicit pregnancies who numbered 5 in the present study. Of the 13 patients in the legitimate group, diagnoses were depressive reaction in 5 patients, anxiety reactions in 6 patients and obsessional neurosis in 2 patients. In the illicit group, diagnoses were borderline defect in 1 patient, depressive reaction in 5 patients, anxiety reaction in 2 patients and psychopath in 1 patient. Of the total group 81.8 per cent. were diagnosed as either anxiety or depressive reactions.

The criterion for diagnosis of essential hypertension was a persistently raised blood pressure reading over 140/90 mm. mercury during several visits to the clinic in the absence of demonstrable pathology to account otherwise for the hypertension. Pre-eclamptic toxæmia was diagnosed in the presence of any two of the following: (a) minimal blood pressure reading 140/90 mm. mercury, (b) albuminuria, (c) oedema in the upper part of the body. Prolongation of pregnancy was accepted if continued for at least 43 weeks; prolongation of labour implies a minimum of 24 hours, whilst the categories of Caesarean section and forceps delivery are self-explanatory, with the proviso that mechanical causes had been excluded. A final category of "difficult behaviour" during labour was included though based on a crude subjective assessment by the attending staff.

Essential hypertension, which shows such a high proportion in the total neurotic group, was found to be equally so throughout the subgroups compared with the subgroups in the Dulwich Hospital controls. Disturbed behaviour is seen to predominate in the group studied, though this datum is difficult to evaluate, as it may reflect biased assessment on the part of the attendants as much as the behaviour of the neurotic patients.

The clinical picture that emerges from the two groups tabulated below, is that the illicit group is characterized by a relative absence of previous mental illness associated with a minimal family history of psychiatric disorder; the pregnancy is unwanted and a temporal relationship exists between the

TABLE II
Clinical Pattern of Psychiatric Illness
 (Percentage figures)

	Illicit Conceptions	Legitimate Conceptions
Total Nos.	9	13
Family history of psychiatric disorder	11.1	46.2
Family history of personality disorder	22.2	23.1
Previous mental ill-health	22.2	69.3
Pregnancy ante-dating neurosis	77.7	46.2
Rejection of foetus	88.8	53.8

pregnancy and the affective disorder. In effect the psychiatric illness is predominantly reactive. The pattern in the legitimate group is comparable with that seen in non-pregnant neurotic patients.

A symptomatic assessment of the psychiatric state was made, the term improvement implying marked resolution. Insufficient data was available on 4 patients. Irrespective of the division into illicit or legitimate primiparae or multiparae, improvement was noticed in 72.2 per cent. of 18 patients, though the illicit group only took 2 months to reach this stage compared with 4.5 months in the remainder. However, of the 22 patients, 3 made suicidal attempts and 2 had suicidal thoughts, divided equally between the illicit and legitimate groups.

DISCUSSION

It seems possible now to answer some of the questions initially formulated. Psychiatrically, a pregnancy supervening in a neurotic patient may cause a temporary exacerbation of symptoms, but as with patients who present a reactive illness to an illicit conception, the prognosis during the months of pregnancy and labour is good. Treatment in the illicit group is essentially supportive and social, acceptance of the patient's pregnant state without a display of moral judgment, sharing responsibility with the patient regarding arrangements for antenatal care and obtaining hostel accommodation if required. The suicidal risk is present initially and might necessitate in-patient admission but there seems little reason to advocate therapeutic abortion on these grounds alone, as psychiatric improvement may be anticipated during the coming months. It must be emphasized that only short-term prognosis has been assessed and this may bear no relationship to puerperal reactions or mother-infant interaction with the possible sequelae of psychological disorder in the child.

The obstetric prognosis for the neurotic patients in the group studied, is characterized by a high proportion of patients with essential hypertension, disturbed behaviour during labour and an absence of abnormalities of labour. The latter findings are supported by other studies. Klein, Potter and Dyke (1953) studied 27 primiparae patients and sub-divided them on the basis of clinical assessment of personality into "stable" and "unstable". They further classified their patient's labour into "psychologically poor or good" and "physiologically poor or good" and were then able to form four categories of patients. They demonstrated that no accurate prediction of behaviour in labour could be made and concluded from their findings that "emotional factors have no palpable effect on the actual mechanics of labour" and that "behaviour in pregnancy was not necessarily duplicated in labour". A better methodological

approach using the Maudsley personality inventory, rating scales and intelligence testing on 200 patients was carried out by Stewart and Scott (1953) and Scott and Thompson (1956). These conclusions were that there appeared little relationship between "behaviour in labour and psychological assessments made in pregnancy" and that patients with a high neurotic score on the Maudsley medical questionnaire failed to show a high incidence of difficult labour. That the group experiences and hierarchical structure of the staff in the labour ward prior to delivery may be of greater aetiological importance in labour abnormality is suggested by Tylden (1952). That personality rather than neurotic symptomatology might be more pertinent to abnormality of labour, receives support from Cramond (1954) who using a control group matched for age, height, marital status, parity, intelligence and social class, studied 50 patients with severe uterine dysfunction. Although finding no significant difference between the two groups comparing "rejection of the feminine role, psychosexual adjustment and anxiety of pregnancy" he described a "dys-function temperament" characterized by "suppression of feelings of tension, reserve, suspicion, difficulty in talking and more conventional than normal".

The finding of essential hypertension in a high proportion (18.2 per cent.) compared with the controls (1.5 per cent.) is of obstetric importance, for McClure Brown (1958) found that in 216 cases of mild hypertension prior to 15 weeks pregnancy, 39 per cent. developed toxæmia and this is now the most common cause of maternal mortality. Professor Pickering (1955) refers to pre-eclamptic toxæmia as "specific hypertensive disease of pregnancy" and argues that it is illogical to distinguish between the two conditions of essential hypertension and pre-eclamptic toxæmia on the basis of finding albuminuria or oedema in the latter. Pickering, although pointing out the many methodological difficulties involved in psychiatric research, considers that environmental factors, including psychological ones, may play a major contributory part in the production of raised blood pressure. Coppen (1958) who psychiatrically studied 50 toxæmic patients with controls found a significant relationship between psychiatric symptoms during pregnancy and the later development of pre-eclamptic toxæmia. Further evidence for this possible relationship is quoted by Dieckman (1952) and Page (1953) who described the dramatic supervation of a blood pressure of 210/140 mm. with albuminuria and fits within twenty-four hours of the patient being arrested for alleged felony, her antenatal examination immediately prior to this being normal. The present author abstracted from the case reports in their monograph by Klein, Potter and Dyke, the patients described as "unstable-neurotic" and found 40 per cent. recorded as hypertensive compared with 11.8 per cent. in the "stable" group. Caldwell (1958) reviewed retrospectively 300 obstetric patients and found 12.2 per cent. of his "neurotic" patients diagnosed as pre-eclamptic toxæmia compared with 4.7 per cent. in the "well-adjusted" group, though his study unfortunately lacks definition of the terms used. There is much literature concerning the studies of hypertension, neurotic mechanisms and personality in non-pregnant patients; Hambling (1951), Binger *et al.* (1945), Wolf *et al.* (1943), Saslow *et al.* (1950) and Reiser *et al.* (1950). It is of interest to note that Saslow *et al.* concluded that "there was a significant association between 'obsessive-compulsive behaviour', 'sub-normal assertiveness' and hypertension", but neither of the 2 patients with obsessional neurosis in the present series developed hypertension during their pregnancy.

The possible neural effect in producing hypertension receives some support from the occasional case reports of lowered blood pressure in hypertensive

patients who underwent leucotomy operations for associated severe psychiatric illness (Partridge, 1950; Tibbetts, 1949). Hofbauer (1956) writing on the neuro-endocrine pattern of toxæmia distinguished two elements. Firstly, the dominant influence of the "hypothalamic-pituitary-adrenal system" and secondly the "functional sensitivity of the arterioles affecting their pattern of response to hormonal stimuli". Walsher (1948) points out that, in addition to neural and hormonal effects producing hypertension, a further indirect mechanism might be the over-eating of the nervous insecure patient. The present author wonders what possible relationship might exist between the "food fads" of pregnant women, toxæmia and hypertension. With increasing awareness of neural and humoral aspects of hypertension one can theoretically conceive of psychological experiences having their physical counterpart at the cortical level and their passing through a physiological pathway via the hypothalamus, post-pituitary and adrenal glands, as well as the more direct neural pathway via the autonomic nervous system.

It is not the author's intention to discuss here in detail possible pathogenic mechanisms relating psychological stimuli, psychiatric symptoms and raised blood pressure. The author considers that for the purposes of clinical research two points require further exploration. Firstly, confirmation of findings by obtaining a larger series of patients. Secondly, to assess whether patients with neurotic symptoms not amounting to a neurosis or requiring psychiatric intervention have an associated abnormally raised blood pressure during pregnancy. With the latter point particularly in mind, the present writer plans to engage upon a statistical and controlled anterospective study; testable hypotheses relating to pre-eclamptic toxæmia and essential hypertension can now be formulated.

SUMMARY

A psychiatric and obstetric study of 22 neurotic pregnant patients reveals a high proportion of patients with hypertension (18.2 per cent.) compared with the controls (1.5 per cent.). No higher percentage of labour abnormalities was noted other than difficult behaviour (13.6 per cent. compared with 2.2 per cent. in the controls), but in the absence of data regarding the interpersonal staff relationships this cannot be adequately evaluated. Affective disorder was the commonest reaction (81.8 per cent.) and a favourable short-term psychiatric prognosis was found in 72.2 per cent. of patients, despite suicidal attempts or thoughts being present in 23 per cent. of the group. Differences in the clinical pattern of the psychiatric illnesses between illicit and legitimate conceptions is presented.

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A CLINICAL TRIAL OF LARGACTIL (CHLORPROMAZINE), STEMETIL (PROCHLORPERAZINE) AND VERACTIL (METHOTRIMEPRAZINE)

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INTRODUCTION

MANY phenothiazine derivatives are now in use in the treatment of schizophrenia. We, in this hospital have used Largactil extensively and more recently Stemetil in the management of chronic schizophrenia.

The latter drug was the subject of a controlled investigation which did not involve the double-blind technique (Milne and Berliner).

Since the above series a new phenothiazine—methotrimeprazine (Veractil) has been recommended by many authorities for the control of schizophrenia.

Veractil bears resemblance to both chlorpromazine and promethazine pharmacologically.

Original clinical investigation carried out by the French suggested that only a quantitative therapeutic difference existed between the two.

According to Deschamps and Madre six out of 14 long-standing female schizophrenics who had previously failed to respond to other forms of treatment were greatly improved—and a further 5 slightly improved.

Lambert, Beaujard *et al.* found in 28 cases of chronic schizophrenia, the response was equivalent to that obtained by chlorpromazine, but disturbed behaviour was not influenced as favourably as with chlorpromazine.

Deschales, Lanteri-Lausa and Fargeon found in 22 cases suffering from chronic schizophrenia, half were slightly improved and the remainder unchanged or worse. They concluded over a larger series that methotrimeprazine was somewhat less effective than chlorpromazine.

Gurtler, Soos, and Haumonte came to the conclusion that in schizophrenia Veractil was palliative and tranquillizing with no effect on the psychotic basis, this being at variance with the effect of chlorpromazine.

In the use of Veractil the above authorities noted an increase of somnolence in their patients. There were no gross extra-pyramidal side-effects but postural hypotension appeared frequently.

The purposes of our investigation were:

1. To compare the relative efficiency of Largactil, Stemetil and Veractil.
2. To substantiate or refute the results of the previous clinical trial of Stemetil undertaken by one of us (H.B.M.) using on this occasion the double-blind technique.

MATERIAL AND METHOD

The patients in this trial consisted of 100 male chronic schizophrenics ranging in age from 17-61. No attempt has been made to classify these patients into a particular type of schizophrenia owing to the high average duration of stay in hospital. All the individuals selected for this trial had previously been receiving treatment with one or more phenothiazine derivatives for a considerable period. Severely subnormal and leucotomized patients were excluded from selection.

The 100 patients were divided arbitrarily into 4 groups of 25 by the chief male nurse using as criteria (1) equivalent average age and (2) equivalent duration of stay in hospital (in years).

The following table gives details of the composition of the groups and previous treatments.

TABLE I

Group	Average Age in Years	Average Duration of Stay in Hospital in Years	Age Span	E.C.T.	Insulin	Largactil	Stemetil
1 ..	38	13	27-61	17	3	25	13
2 ..	43	13	17-57	18	6	25	11
3 ..	46	15	25-58	16	7	25	9
4 ..	42	12	27-60	17	8	25	15

It was decided to use the following dosage scheme at the commencement of the trial:

- (a) Largactil 75 mg. t.i.d.
 (b) Stemetil 25 mg. t.i.d.
 (c) Veractil 50 mg. t.i.d.

the dosage of each was selected on the basis of previous and reported clinical experience.

Identical tablets were used.

The pharmacist made the initial allocation of individual active drug and inert tablet to each group in particular.

It was further decided, at the commencement of the trial that if a particular group obviously showed persistent signs of deterioration due to being on a placebo, the pharmacist would (1) add an active drug to this group, (2) by further manipulation add an inert tablet to leave the active dosage of Stemetil intact, and (3) double the dosage of the Largactil and Veractil groups.

Prior to the commencement of the trial, which was of 24-weeks duration, each group was allowed to settle in their new and uniform environment. During this period routine blood chemistry, urine analysis, basal blood pressure, body temperature and weight were noted. During the trial pulse and temperature were recorded diurnally and blood pressure daily, for the first week and

thereafter every 3rd week until the end of the trial. The blood chemistry—including liver function tests—was repeated at similar intervals. The weight was recorded weekly.

The nursing staff were requested to note any specific side-effects. Patients were allowed parole again when the initial period of deterioration was reversed and were encouraged to take part in occupational therapy and other social activities.

Behaviour was assessed by the nursing staff using a behaviour rating scale described by Baker and Thorpe and used by one of us in a previous trial (Milne and Berliner).

This commenced while each group was on routine treatment.

The nursing staff marked each patient's behaviour daily from Monday to

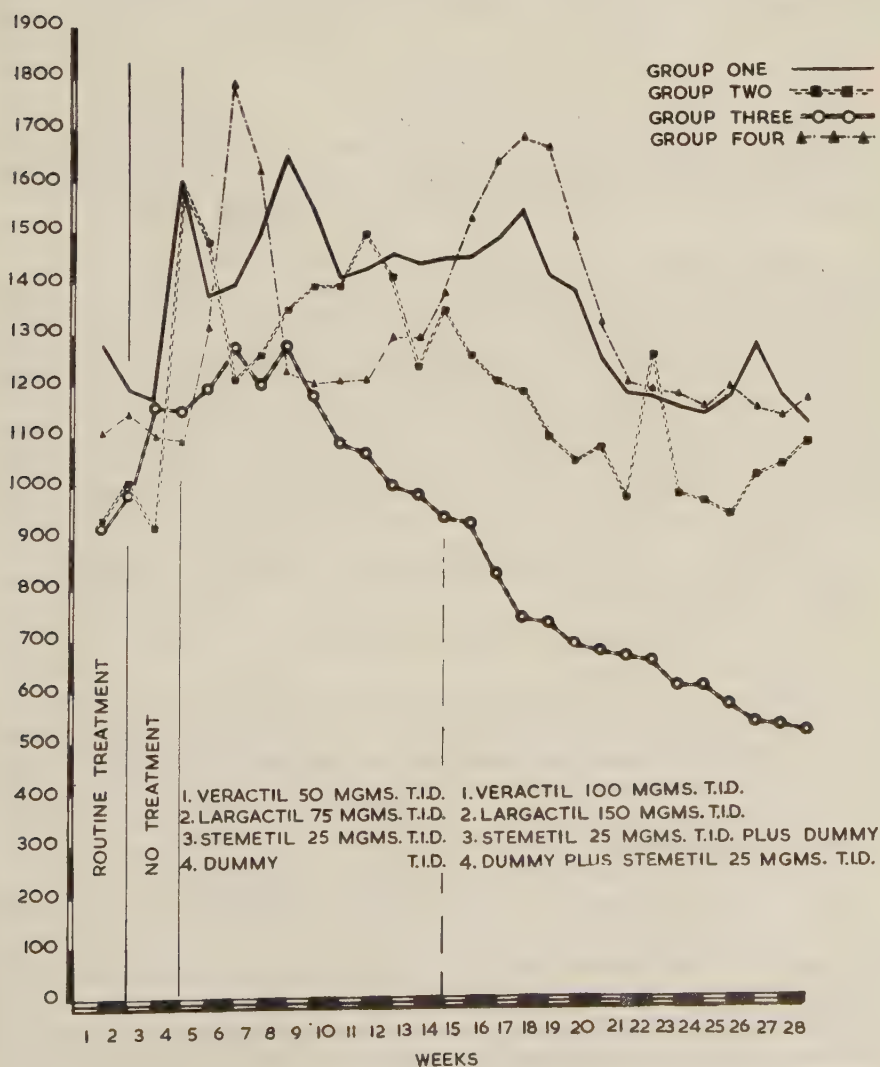


FIG. 1

Friday. The daily scores in each group were summated weekly both for individual factors and overall behaviour.

The weekly total group scores were graphically represented as shown in Figure 1.

Individual factorial scores although not charted will be commented upon. Active routine therapy was withdrawn abruptly for a period of two weeks, which was found to be of sufficient duration to allow measurable deterioration of behaviour. It is of interest to note in this series, as in the previous trial, that within 2 weeks of withdrawal of an active preparation there was marked deterioration of behaviour of the chronic schizophrenic. This observation which has been repeatedly seen in other cases not included in this trial is in direct contradiction to the evidence presented by Good, MacSterling and Wayne Holtzman who state that chlorpromazine can be withdrawn from chronic schizophrenic patients for at least 10–12 weeks without any noticeable regression in behaviour or intellectual functioning.

RESULTS

As the objects of this trial were two-fold, i.e. (1) to compare the relative efficiency of Largactil, Stemetil and Veractil and (2) to substantiate or refute the results of the previous clinical trial of Stemetil—we propose to analyse our data (a) by individual group and (b) by a comparison of groups.

(a) *Individual Groups*

Group 1. (Tabs. Veractil 50 mg. t.i.d. for 10 weeks—increased to 100 mg. t.i.d. for remainder of trial.)

There was an initial further deterioration in behaviour lasting four weeks followed by a relative improvement up to the point at which the dosage was doubled. From this date behaviour improved until at the end of the trial the total weekly behaviour was equivalent to that which obtained at the commencement. Analysis of individual factors corroborated this lack of improvement and further analysis did not substantiate an increased drowsiness reported by other authors.

Clinically it could be said that all members of this group came under the heading of no improvement.

Group 2. (Tabs. Largactil 75 mg. t.i.d. for 10 weeks—increased to 150 mg. t.i.d. for remainder of trial.)

Following initial dosage there was an immediate improvement in the first week—probably due to a placebo effect—which was followed by a deterioration lasting 5 weeks and then a steady improvement occurred following the increase of dosage to 150 mg. t.i.d.

At the end of trial the behaviour rating was approximately similar to that at the commencement.

Analysis of individual factors confirmed a lack of response.

As in Group 1 the clinical results for individual members came under the heading of “no improvement”.

Group 3. (Tabs. Stemetil 25 mg. t.i.d. for 10 weeks—then combined with dummy tablet for remainder of trial.)

Following initial dosage there was some deterioration over a period of four weeks followed by a steady and progressive response to treatment up to 10 weeks at which time the rating was lower than at the commencement.

Following the introduction of dummy there was no obvious dramatic fall and in fact the rating continued to drop until the completion of the trial at which time the behaviour score was approximately half the original.

Analysis of individual factors showed this to be due to a response in Factors A, G and L (Baker and Thorpe).

Factor A—concerned with the phenomenon of somnolence.

Factor G—concerned with the property of spontaneous speech.

Factor L—concerned with the ability to make friends.

It is of interest to note that in the previous clinical trial of Stemetil, improvement was also noted in the similar constellation of factors.

Clinically it was observed that improvement in this group was largely measured by an increase in tidiness, personal hygiene and willingness to work without supervision. Patients who had been previously asocial and monosyllabic became friendly and comparatively voluble. In this group the results could be summarized as follows:

Discharged	..	..	..	..	..	..	..	2
Much improved	..	..	..	..	..	..	..	6
Improved	..	..	..	..	..	..	..	11
No change	..	..	..	..	..	..	..	6

Group 4. (Dummy tabs. t.i.d. for 10 weeks—then combined with Stemetil 25 mg. t.i.d. for remainder of trial.)

Following initial dosage there was marked deterioration lasting 1 week only. This followed by a dramatic improvement over the next three weeks which was in our opinion a placebo response. Behaviour then steadily deteriorated over the next five weeks at which juncture the pharmacist decided to intervene and introduced Stemetil 25 mg. t.i.d.

The behaviour continued to deteriorate for a further 3 weeks and then steadily improved. At completion of trial the rating was equivalent to the original but the duration of active therapy was only 14 weeks as opposed to 24 weeks. It was felt that further improvement would have taken place if the trial had been prolonged.

Analysis of individual factors confirmed this lack of response.

Clinically the results for individual members came under the heading of "no improvement".

(b) *Comparison of Groups*

The relative efficiency of our three active preparations, according to behavioural analysis, suggests that in the long-term treatment of chronic schizophrenia Stemetil is most efficient. It would appear that Largactil is of secondary importance and finally Veractil of little value.

Further it would seem that the Veractil response was equivalent to treatment with placebo. It does seem apparent that doubling the dosage of Largactil and Veractil did produce an increased efficiency.

It will be seen that there was no alteration in dosage in Group 3 and equating this dosage (25 mg. t.i.d.) against a maximum dosage of Largactil 150 mg. t.i.d. and Veractil 100 mg. t.i.d. would completely confirm the previous observations on the efficacy of Stemetil in much smaller dosages. It has been previously suggested that the active dosage of prochlorperazine is one-third of the active chlorpromazine level. It would appear therefore that this has been an underestimation.

No statistical evidence has been produced in this trial although statistical analysis of the results has been made.

The graph in itself shows the significant findings. The statistician who surveyed our results commented upon one fact. On analysis of daily factorial scores he found a regular deterioration in rating from Monday to Friday each week. We feel that this was probably due to a fatigue element in the nursing observers.

Side-Effects and Complications

This series was distinguished by the absence of side-effects. When occurring they were of minimal importance.

Group 1—there were two hypotensive attacks occurring in the 2nd and 3rd week of therapy.

Group 2—no side-effects.

Group 3—no side-effects.

Group 4—hypotensive attack while on placebo—which therefore can be discounted.

One patient developed Parkinsonism whilst receiving placebo plus Stemetil.

Analysis of blood chemistry and liver function tests showed an interesting feature. Four cases in Group 4, while on placebo, developed positive thymol flocculation, and turbidity and a positive Van den Bergh response. It can only be presumed that this was a sub-clinical infective hepatitis.

It can be emphasized that contrary to many authors there appears to be little danger of extra-pyramidal side-effects while using Stemetil at this level.

It will be seen that out of 50 patients receiving Stemetil in this series there was only one case of Parkinsonism.

SUMMARY

A comparison of the relative efficiency of three drugs—Largactil, Stemetil and Veractil—was undertaken. It was found that of these agents Stemetil was the most efficient, followed by Largactil and Veractil in that order. We have not been able to confirm the therapeutic efficiency of Veractil in the treatment of chronic schizophrenia.

By using the double-blind technique we have confirmed our initial observations regarding the mode of action of Stemetil.

The trial was characterized by the low incidence of side-effects.

ACKNOWLEDGMENTS

We would like to thank Dr. E. U. H. Pentreath, Medical Superintendent, Pastures Hospital, Derby, for his permission to publish this series, the nursing and laboratory staff for their invaluable help and also Mr. L. Banyard, B.Sc., for his statistical advice.

Our thanks are also due to May & Baker Ltd., for their co-operation.

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THE USE OF DATA FROM LOW FREQUENCY ANALYSIS TO ILLUSTRATE SERIAL EEG CHANGES IN DEPRESSED PATIENTS DURING TREATMENT WITH IPRONIAZID

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IPRONIAZID, introduced as an anti-tubercular drug, has been widely used in the treatment of depression. It is a monoamine oxidase inhibitor and some of its effect on the central nervous system may therefore depend upon its preventing the breakdown of serotonin. It is hepatotoxic. Dally (2) and many others have commented upon a time lag of at least a week after the start of treatment before observable clinical improvement in depressed patients.

Martini *et al.* (5) reported variable EEG changes and concluded that the drug "was not shown to induce important changes in the EEG". Agin (1) reported no change in the EEG in 85 per cent. of cases before and after treatment with iproniazid and in the remaining 15 per cent. found a slowing of the frequency and increase in amplitude. Both these investigators carried out serial EEGs but both relied upon visual inspection of the primary trace.

METHOD

During a clinical trial of iproniazid serial EEGs were taken before treatment and at weekly intervals thereafter in 10 cases of depression. Iproniazid was the only drug used and the female patients were all post-menopausal. Tracings were made over a minimum period of five weeks and in one case, which is to be specially considered, over a period of twelve weeks. Records were taken fasting on the same day of the week and at the same time of day.

In the first 4 cases visual inspection of the primary trace was the only method used. J.H.M. had the impression that there might be slowing of the dominant frequency but the degree of change was unconvincing and certainly not objectively demonstrable.

In the next 6 cases a Burden Neurological Institute Low Frequency Wave Analyser was used throughout, the analyser write-out being obtained from bipolar recording in the right temporo-occipital region. Continuous analysis was carried out during the 30 minutes of recording time used for each tracing.

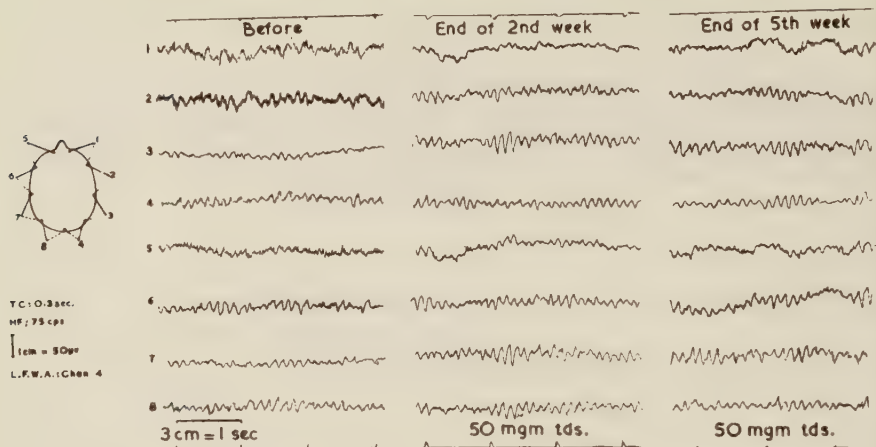


FIG. 1.—No obvious serial changes in primary tracings. Patient on iproniazid 50 mg. t.d.s. throughout.

From each record five separate epochs of 10 seconds were selected during periods when the eyes were closed, though not within 5 seconds of eye closure, and when the tracing on visual inspection was considered to be artefact free.

Frequency distribution curves were constructed by joining the tops of the analyser write-out (Fig. 2a). Galton's (4) overlay technique which has already been successfully applied by Dawson (3) in an electrophysiological context, was then used and the five distribution curves for each record superimposed, thus providing in effect a graphical representation of correlation (Fig. 2b). The composite curves from each individual tracing were now compared in the serial series of records obtained from each patient.

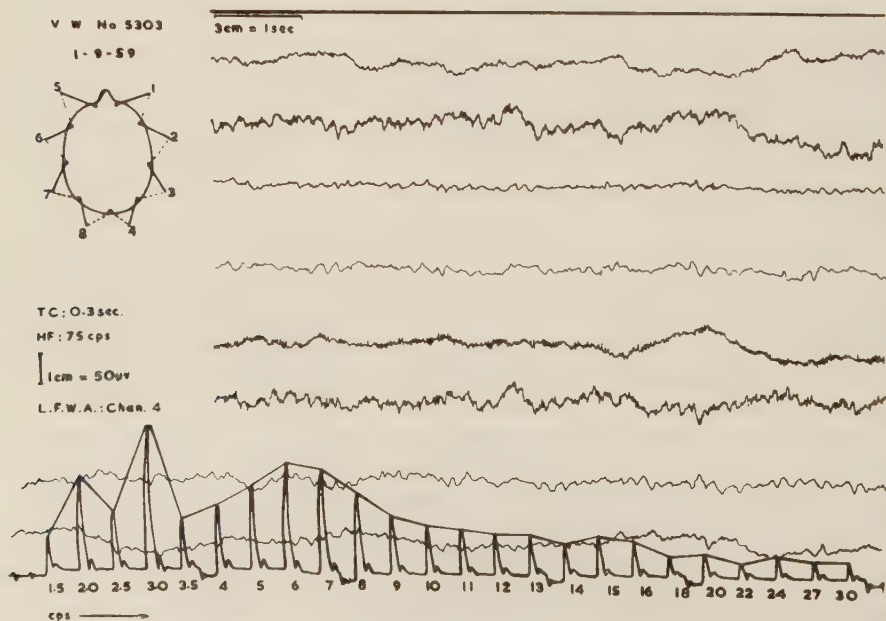


FIG. 2a.—Frequency distribution curve for one 10-second epoch.

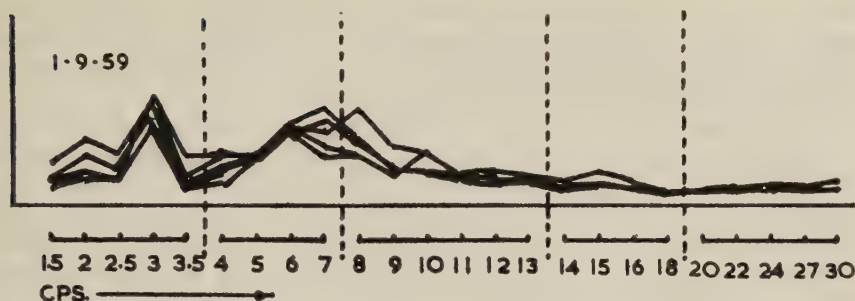


FIG. 2b.—5 frequency distribution curves from the same record superimposed.

RESULTS

In all cases there is an obvious slowing of the dominant frequency with an associated reduction of amplitude in the alpha (8–13 c./sec.) range. In view of the time lag reported in the clinical response to the drug, it is of particular interest that this slowing is first evident at the beginning of the third week. This is illustrated in Figure 3 which shows the composite record from serial tracings in one patient over a period of 12 weeks. It is perhaps worth noting that in this case a reduction by half in the iproniazid dosage at the end of the sixth week is followed by a gradual quickening of the EEG.

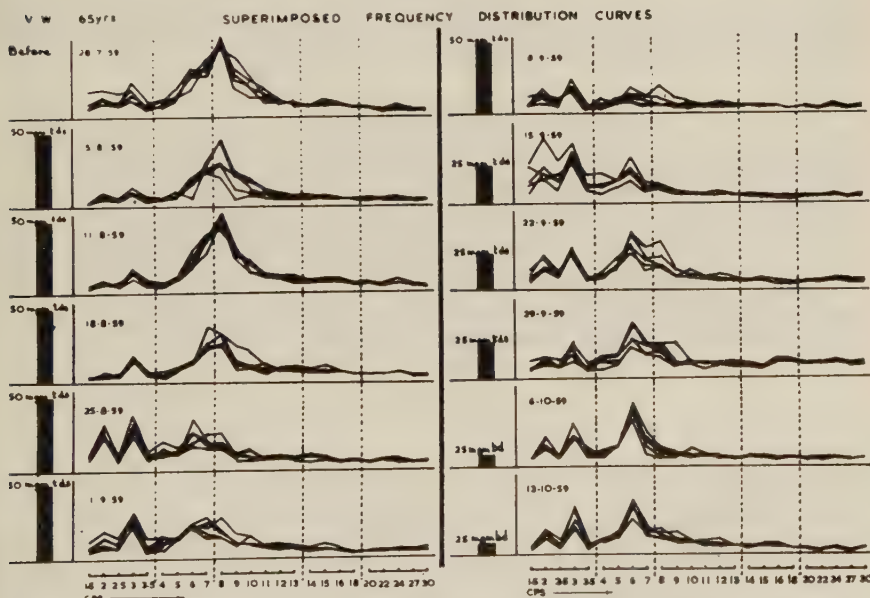


FIG. 3.—Series of composite curves (2b) at weekly intervals over a period of 12 weeks. Note gradual change after halving iproniazid dosage on 9 September, 1959.

DISCUSSION

The evidence from this series is that three weeks after the administration of iproniazid there is a clearly demonstrable alteration in the electrical activity from the human brain, the most obvious component of which is that the dominant frequency is slower. Speculation as to the causes of the slowing must

include the consideration that non-specific EEG changes of a relatively crude nature have been described by Parsons-Smith *et al.* (6) in cases of hepatic insufficiency but biochemical investigations carried out *pari passu* in the present study offered no support for such a view.

There appears to have been no previous report of analyser data from the primary trace being dealt with in the way described and it is suggested that the method may well have general application as for instance in inter-group comparisons of people with mental disorder. There was an impressive stability of output in the present series which poses the question as to whether such stability is a feature of the diagnostic group considered or may have more general application. Serial studies of normal controls are therefore being undertaken using the same technique.

SUMMARY

A method is described of superimposition of analyser data from EEG tracings which, when applied to serial records in a group of patients suffering from depressive illness under treatment with iproniazid, enables the convincing demonstration of slowing of the dominant frequency three weeks after the commencement of therapy. It was not possible to get this information by visual inspection of the primary tracings. It is suggested that the method may have more general application.

ACKNOWLEDGMENT

It is a pleasure to thank Dr. R. Ström-Olsen, Physician Superintendent of Runwell Hospital, by whom these patients were treated personally, not only for making this study possible but also for his help and encouragement.

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VOLVULUS OF THE COLON IN THE DEMENTED PATIENT

THE PRESENTATION OF FOUR CASES AND A REVIEW

By

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IN spite of a thorough search of the medical literature in this country we have been able to discover only two articles (1, 2) that come within the scope of this paper and these were descriptions of single cases in elderly men at the end of the last century. As it is commonly stated in medical text books that not more than 10 per cent. of all cases of intestinal obstruction are due to volvulus and that of these up to 70 per cent. occur in men, we have been impressed by the incidence of four cases of volvulus in just over three years on the female side of this mental hospital (536 females of all ages).

CLINICAL MATERIAL AND CASE REPORTS

(a) *Case Material*

The four patients who developed volvulus had an average age of 64 years, were all suffering from fairly advanced dementia (two were seniles and two chronic schizophrenics) being incapable of conducting a conversation or looking after their basic needs such as feeding or toilet without considerable nursing supervision. On these criteria we decided to assess the incidence of such deteriorated patients on the female side of the hospital as it seemed from the literature that volvulus was much more likely to occur in this particular type of patient. Our assessment showed that 286 or 53 per cent. of our female patients were demented. 45·6 per cent. of this group were diagnosed as suffering from senile dementia, 39·2 per cent. were chronic schizophrenics, 11·9 per cent. mentally deficient and the remainder of 4·1 per cent. suffered from epilepsy or other organic states associated with dementia. The average age of the whole group was 67 years.

(b) *Case Reports*

The first case. A woman of 64 years who had been 25 years in hospital suffering from chronic schizophrenia. She was apathetic, rambling in conversation and almost inaccessible. She suffered from myocardial degeneration. Periodically she required cascara tablets for constipation. In September, 1952 she complained of griping abdominal pain and vomited a number of times. This condition settled in a few days. On 25 July, 1956 there was a history of two days' abdominal pain and distension with constipation. On 27 July, 1956 her abdominal distension was more marked and there had been occasional vomiting in the previous 24 hours and no result from enemas. She was admitted to a general hospital as a case of large bowel obstruction. At operation a gangrenous volvulus of the pelvic colon was found due to twisting of the pelvic mesocolon $2\frac{1}{2}$ times. She made a good recovery.

The second case. A woman of 65 years who had been in hospital suffering from senile dementia for three years. She was incapable of coherent conversation, incontinent and recognized as suffering from chronic constipation for which she frequently required aperients and periodically an enema. The nurses were in the habit of taking her to the toilet three times daily as she was incapable of going there on her own initiative. Her physical condition was satisfactory. Since 1955 she had been receiving a tranquillizer continuously in moderate dosage. The nursing staff had noticed that she had periodic abdominal distension for several months prior to the onset of her illness. On 15 February, 1958 her abdomen was noticed to be markedly distended. The nurse stated that she had been restless for a couple of days and

had been refusing food but taking fluids. There was no history of pain or vomiting and her abdomen was soft on palpation. Several enemas produced no results. She was transferred to a general hospital and at operation volvulus of the pelvic colon was found with two complete turns. Part of the pelvic colon was resected and she made a good recovery.

The third case. A woman of 76 years who had been in hospital for 10 years suffering from senile dementia. She was a noisy, disorientated, inaccessible patient who suffered from cardiovascular degeneration. She had been continuously on heavy doses of barbiturates and tranquillizers since 1954. She was recognized by the nursing staff as suffering from chronic constipation and had been receiving mag. sulph. and an enema weekly for many months. She had to be taken to the toilet as she was incapable of going there herself. On 28 May, 1959 she developed cardiovascular collapse. There was no result from enemas. A diagnosis of acute large intestinal obstruction was made but her general condition was too poor for operation and she died 20 hours after the onset of her illness. At post-mortem acute right ventricular failure with volvulus and gangrene of about two feet of pelvic colon was found.

The fourth case. A woman of 51 who had been 19 years in hospital. She was a case of chronic schizophrenia who was deluded, hallucinated and incoherent. She had been receiving mag. sulph. weekly as an aperient for some time. Since 1955 she had been continuously on moderate doses of several different tranquillizers. Her physical condition was satisfactory. On 12 October, 1959 her abdomen was noted to be distended but soft on palpation. On 13 October, 1959 there was still no history of pain or vomiting but her appetite was impaired though she took fluids readily. As her abdomen had become more distended and tympanitic and there was no result from enemas she was transferred to a general hospital. At operation volvulus of the pelvic colon was found which was not gangrenous, and resection and end to end anastomosis was carried out. She made a good recovery.

INCIDENCE AND AETIOLOGY

Sweet (3) analysed 520 cases of acute intestinal obstruction (exclusive of strangulated external herniae) at the Massachusetts General Hospital from 1873 to 1930 and found that volvulus of small and large bowel accounted for 53 or 10 per cent. of the total. Michel and McCafferty (4) reported on 119 cases of acute obstruction of the large bowel at two hospitals over a period of 12 years with 24 cases of volvulus of which 19 involved the sigmoid colon and three the caecum. They state that volvulus is a relatively infrequent cause of intestinal obstruction in the United States and Western Europe where it accounts for not more than 10 per cent. of all varieties of obstruction in all parts of the gut. In Finland, Russia and Eastern Europe on the other hand they maintain that it accounts for from 30–50 per cent. The explanation of this remarkable discrepancy they believe to lie in the nature of the diet of most Eastern European countries which is high in vegetables and residue and they maintain that further confirmation is supplied by the notable increase in the incidence of volvulus as a result of war-time diet in which these foodstuffs bulked higher than they did in peace time. In support of this 85 of 102 patients with volvulus reported by Bruusgaard (5) in 1947 were treated after September, 1939. Of the total 102 cases, 91 or 89.2 per cent. were volvulus of the sigmoid colon. Michel and McCafferty (4) also state that there is often present excessive mobility of the affected part of the bowel as a result of a long freely movable intestinal mesentery, a relatively short mesenteric root and an increase in length of the intestinal loop. They maintain that clockwise torsion of the sigmoid up to 180° does not usually give rise to symptoms and corrects itself spontaneously. With clockwise torsion over 180° or anti-clockwise torsion of any degree, events depend on the degree of twist. If it is of moderate degree and occurs slowly the pathological process may be limited to simple obstruction for several days. If, however, it is of considerable degree and particularly if it occurs rapidly strangulation occurs because of the sudden interference with the blood supply to the gut. If torsion remains uncorrected the end result is gangrene of the wall, perforation and peritonitis in all cases.

Norback (6) reports 23 cases treated at a surgical department over a

period of 19 years. He states that 35 per cent. of the patients had shortly before undergone operation for herniae which he believes had its origin in chronic constipation. He also relates that 30 per cent. of the series were cases of severe mental disorder, who had spent between 19 and 51 years as bedridden patients in mental hospitals. He was of the opinion that the most likely explanation for the high incidence of volvulus in chronic mental hospital cases was pronounced constipation which is likely to occur in bedridden patients who are unable to complain or control defaecation. The chronic constipation giving rise to dilation and elongation of the sigmoid colon thus providing conditions for torsion.

Dean and Murray (7) who treated 21 cases of volvulus of the sigmoid colon during a five-year period also found that 71.4 per cent. of the cases were patients in an institution for mental care. 66.6 per cent. of the cases were male and the average age of the group 55 years. In a discussion on this paper before a surgical association, Dr. J. C. Owings (7) reported on 25 cases of volvulus stating "almost all these cases have been in mental hospitals", and he goes on to state, "I do not know whether or not there is any direct connection to the diet or any connection between the mental changes and the recurring volvulus together with the large megacolon". There is a much higher incidence of volvulus in almost all recorded cases in men and the lower incidence in women has been attributed to the wider female pelvis and the greater relaxation of the abdominal wall (particularly in those who have borne children) affording greater opportunities for spontaneous reduction of any torsion that may occur.

Volvulus is a condition of later life and in the colon the sigmoid is by far the commonest site. (Bruusgaard in his series records 89.2 per cent.) Volvulus of the caecum is uncommon and tends to occur in a younger age group. Michel and McCafferty (4) record 3 cases in a total of 24 of large bowel volvulus, an incidence of 12.5 per cent. which is higher than in most reported series. The average age of the cases being 28.3 years. Volvulus of the transverse colon is extremely uncommon. Bruusgaard (4) reported only 14 in 438 collected cases of volvulus of the colon.

DISCUSSION

Volvulus of the colon in later life appears to occur almost exclusively in the sigmoid area. Of the 24 cases described by Michel and McCafferty (4), 8 patients had a definite history of previous acute attacks and nine others had chronic symptoms of intestinal dysfunction. Dean and Murray (7) in describing 21 cases of volvulus of the sigmoid colon maintain that a background of chronicity occurred in 17 of the cases and that 18 of this series eventually developed acute volvulus. Chronic sigmoid volvulus is usually characterized by recurrent exacerbations of painless abdominal distension, visible peristalsis, constipation and periods of partial decompression, and more complete evacuation by means of enemas. The symptoms of chronic volvulus are often so benign that in the demented patient they are quite likely to be overlooked by the nurse and even the doctor or diagnosed so late that the condition has become one of acute volvulus with the risk of a gangrenous bowel and as a result a much more serious prognosis. Acute volvulus is associated with a tense distended abdomen, visible peristalsis with severe cramp-like pain, dehydration and toxicity. For some days prior to this acute clinical picture there is often a

history of constipation and increasing abdominal distension. All of our four cases of volvulus occurred in the pelvic colon. In one of them there was a history suggesting a previous acute attack though less severe which resolved itself spontaneously and in another a history resembling chronic volvulus for some months before the onset of the acute illness. Two of our four cases presented in a very benign manner with symptoms of abdominal distension, constipation and reluctance to take food. In only one case was the picture one of acute volvulus and the rapid onset of cardiovascular collapse in this elderly woman could easily have led to a mistaken diagnosis of acute heart failure had the abdominal symptoms not been noted early.

There appears to be some doubt as to the reason for the increased incidence of volvulus of the colon in the long-stay mental hospital patient. We believe that chronic constipation is likely to be a major factor in the production of volvulus of the sigmoid colon in the demented patient of the type we have described. The vast majority of these patients suffer from dyschezia which originates in neglect to respond to the call to stool as a result of their deteriorated mental condition. The conditioned reflex upon which defaecation normally depends is thus gradually lost. While a diet of high residue and vegetable content is a stimulus to peristalsis and helps to relieve constipation in the normal patient, in the demented patient whose bowel habit has been lost, it tends only to worsen the condition. Nowadays these patients are kept ambulant whenever possible but we suspect in the past many of them were confined to bed for long periods which increased the tendency to constipation. Over the years constipation has been a particular problem in the epileptic wards in mental hospitals and this was presumably chiefly due to the continuous use of heavy doses of anticonvulsant drugs. Sedative drugs in general have a constipating effect on patients if given over a long period and we are of the opinion that many of the disturbed chronic psychotic patients in the past who received large doses of bromides and barbiturates habitually suffered in this way. Three of our four patients had been on one or more of the tranquillizing drugs for a long time. These drugs are being used in a high percentage of our senile and chronic schizophrenic patients where they are helpful in relieving such symptoms as restlessness and emotional instability and we think that they will continue to be used for this purpose in future. These phenothiazine derivatives are well known to promote constipation in many patients and their analgesic and anti-emetic properties may well mask many of the symptoms of volvulus in the patients who are on them. The nursing staff at this hospital to whom we have spoken are unanimous in their agreement that since the tranquillizing drugs have come into common use in their wards, there has been an increased tendency towards constipation. This whole problem of constipation with its causes, treatment and relationship to volvulus is a very wide one since it not only involves the demented population of mental hospitals but also all long-stay hospitals that care for elderly patients where nursing help is often very short. The most important factor in the prevention of chronic constipation it seems to us is the necessity of impressing upon the nursing staff that many of these patients have lost the desire to go to stool and that they require to be brought to the toilet after meals several times a day whether or not they defaecate in an endeavour to habit train them. Many of these patients will also require regular aperients, periodic enemas and suitable exercise as well as a diet that is not too bulky containing adequate fluids and such substances as fresh fruit which tends to relieve constipation.

SUMMARY

Four cases of volvulus of the colon amongst the demented population on the female side of a mental hospital have been described. Aetiological factors stressed were the high incidence in long-standing mental hospital patients, the relationships to diet and constipation, a preponderance in men, the location of the condition almost exclusively in the sigmoid area of the colon in the elderly patients and frequently a previous history of intestinal dysfunction. It has been suggested that the increased use of tranquillizers predisposes to constipation, is likely to mask symptomatology, and that many of the demented patients in whom volvulus is likely to occur have lost the bowel habit and require habit training. The importance of this and other forms of treatment in relationship to the care of the elderly in institutions was stressed.

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LYSERGIC ACID DIETHYLAMIDE (LSD-25)
XXXI. COMPARISON BY QUESTIONNAIRE OF
PSYCHOTOMIMETIC ACTIVITY OF CONGENERS ON
NORMAL SUBJECTS AND DRUG ADDICTS*

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A GENERALLY acceptable method of comparing psychotomimetic compounds has apparently not been devised. A method of this type would provide the replicability not now available in the newly developed field of psychopharmacology. For example, the method employing the Cold Spring Harbor questionnaire devised by the writer and his co-workers has been criticized as being "too suggestible", "too structured", or "insufficiently cognizant of unconscious processing". It is the purpose of this communication to show that the Cold Spring Harbor questionnaire (1, 2) provides a suitable method of study of the psychotomimetic drugs similar to d-lysergic acid diethylamide (LSD-25). The basis for this statement is the comparison made here of the results of an independent study of a series of congeners of LSD-25 made by Isbell, Miner and Logan (3) in another laboratory, in a different milieu, and on a different population sample. It has been found that the comparative effectiveness of a series of LSD congeners both at Cold Spring Harbor and at Isbell's laboratory in Lexington, Kentucky are the same when the Cold Spring Harbor questionnaire is employed.

COMPARISON OF PROJECTS

Questionnaire. The questionnaire employed at Cold Spring Harbor was that described in detail in a previous paper of this series, and has been in use for eight years (1). The Kentucky project employed essentially the same questionnaire with the questions arranged somewhat differently. However, the differences between the two questionnaires are negligible.

Subjects. The Cold Spring Harbor subjects were the five non-psychotic, white subjects used for the past five years in intra-subject studies. They were an engineer, a physician, lawyer, teacher, and housewife. At Lexington the subjects were all Negro, male, drug addicts, serving for violation of the Narcotic Laws. They were in good physical health with no evidence of a major psychosis.

Drugs. The congeners of LSD studied were obtained from the same source, Sandoz Pharmaceuticals, Hanover, N.J. At both laboratories fresh solutions of all drugs were administered to subjects in a fasting state as follows: at Cold Spring Harbor the drugs were administered one-half hour before dinner; at Lexington they were given in the morning before breakfast. At Cold Spring Harbor doses were not calculated on the basis of body weight but were given in units of round numbered increments, depending on the threshold dose. At Lexington, doses were calculated in micrograms per kilogram. Experiments

* This project has been aided by grants from the Josiah Macy, Jr. Foundation, New York City, New York, and Sandoz Pharmaceuticals, Hanover, New Jersey.

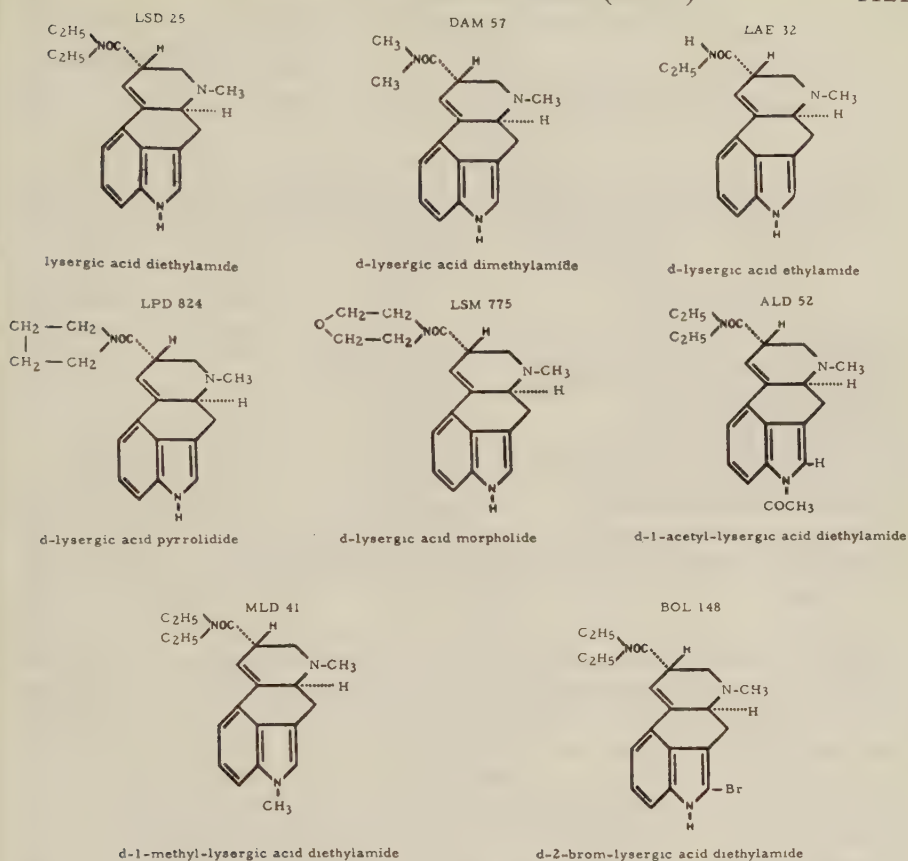


FIG. 1

were usually "single blind" at Cold Spring Harbor, whereas at Lexington neither the subjects nor the observer knew the nature of the drugs under study.

General Conditions. At Cold Spring Harbor the experiments were conducted in the home of the writer, under social conditions designed to reduce anxiety (4), whereas at Lexington they were conducted in a special ward devoted to research. The Lexington patients entered the ward in the afternoon prior to the experiment. They were housed in individual rooms but were allowed to leave them and mix with other patients in a common dayroom. At both places experiments were done at weekly intervals. At both laboratories dosages were increased, but to different levels. At Cold Spring Harbor the purpose was to determine the reactivity of the drugs at or near threshold levels, whereas at Lexington a somewhat different procedure was used. The dosage at Lexington in the first trial was always 0.5 microgram per kilogram. This was increased with the congeners of LSD until at least 50 micrograms per kilogram had been reached without evidence of any psychotomimetic reaction. In both laboratories the congeners were compared with LSD, which was administered from time to time.

Analysis of the Data. In both cases the number of positive responses to the questionnaire was the basic method of computation, although at Lexington the short mental rating test provided by Part II of the Cold Spring Harbor questionnaire was apparently omitted but was substituted by a clinical grading.

RESULTS

The approximate equivalent psychotomimetic doses shown under Table I under Lexington were obtained by Isbell *et al.* by inspecting the data on the

TABLE I

Comparison of Relative Values of Effectiveness of LSD Congeners on Narcotic Addicts (Lexington) and Non-psychotic Subjects (Cold Spring Harbor) Using the Cold Spring Harbor Questionnaire

Compound	Code	Lexington	Cold Spring Harbor
d-Lysergic acid diethylamide	LSD-25	100	100
d-1-Acetyl lysergic acid diethylamide ..	ALD-52	100	91
d-1-Methyl lysergic acid diethylamide ..	MLD-41	33	36
d-Lysergic acid morpholide	LSM-775	11	11
d-Lysergic acid dimethylamide	DAM-57	10	11
d-2-Brom-lysergic acid diethylamide ..	BOL-148	<2	7*
d-Lysergic acid pyrrolidide	LPD-824	10	5
d-Lysergic acid monoethylamide	LAE-32	5	3

* There is variation in different samples of BOL (see, Baron, M. O., Sklarofsky, B., Fremont-Smith, N., and Abramson, H. A., "Lysergic Acid Diethylamide (LSD-25): XXVIII. Assay of 2-Bromo-Lysergic Acid Diethylamide by the Siamese Fighting Fish", *J. Psychol.*, 1958, 46, 303.)

number of positive answers and clinical grading and selecting the dose of the new drug which most nearly approximated the effect seen or expected from one microgram per kilogram of LSD. These data are obtained from Table I of their paper and give the relative psychotomimetic activity of LSD-25=100.

The method of obtaining the relative activity of congeners of LSD-25 at Cold Spring Harbor was described previously. Briefly, it consists of adding the number of positive responses obtained by means of the questionnaire for three and one-half hours after the drug has been administered (at $\frac{1}{2}$ hour, $1\frac{1}{2}$ hours, $2\frac{1}{2}$ hours, $3\frac{1}{2}$ hours). The sum of the number of positive responses, n , is divided by the dose in micrograms and a Response Index= $R.I.=\frac{n}{mcg}$ is calculated using an experimentally determined value of the threshold dose. For a given dose, therefore, the higher the value of R.I., the greater the response to the drug as measured by the questionnaire. Values of the R.I. for the congeners were obtained similarly, and rather than estimating response as Isbell *et al.*, did by approximating reactions equal to one microgram per kilogram of body weight, group averages of the Response Index for the five non-psychotic subjects were compared and recalculated for the value of the R.I. obtained for LSD=100. The raw data and the method of calculation have already been published (4). In Table I the Cold Spring Harbor data are compared with those of Isbell.

DISCUSSION

It is remarkable that the order of activity obtained for the series of LSD congeners at Lexington and Cold Spring Harbor are almost identical, with the exception of BOL-148. The work of Isbell, Miner and Logan, therefore, confirms the procedure employed in this Laboratory and indicates that a greater degree of validity can be ascribed to the method of calculation of the comparative effectiveness of these compounds than had hitherto been supposed. Isbell, Miner and Logan's data also indirectly confirms the validity of the

procedure of calculating the R.I., which forms the basis of our calculation of a Tolerance Index*.

SUMMARY

Data of Isbell, Miner and Logan on Negro narcotic addicts at Lexington, Kentucky are compared with normal non-psychotic, experienced, white test subjects at Cold Spring Harbor. The experiments were performed with a series of congeners of d-lysergic acid diethylamide. The method of comparing the comparative psychotomimetic effectiveness was based upon the use of a questionnaire. Within the limits of error remarkable agreement was obtained on the two different test groups under different experimental settings. The agreement confirms the validity of the method employing the Cold Spring Harbor questionnaire in studies on the comparison of psychotomimetic activity.

* A Tolerance Index may be calculated to compare cross-tolerance produced by different agents. For example, taking the Response Index for LSD as a standard, the ratio of the Response Index for LSD to the Response Index for a test drug will always be more than one if LSD produces the greatest response. We may take, therefore, a measure of effectiveness of cross-tolerance production by MLD to LSD as $\frac{.47}{.02} = 23.5$, a number expressing the apparent effectiveness of tolerance production not corrected for the dosage of MLD. In the particular experiment the Tolerance Index corrected for dosage turned out to be 20.6, which actually is about ten times that found for BOL. (For data see Abramson, H. A., Sklarofsky, B., Baron, A. B., and Fremont-Smith, N.: Lysergic Acid Diethylamide (LSD-25) Antagonists: II. Development of Tolerance in Man to LSD-25 by Prior Administration of MLD-41 (1-Methyl-d-Lysergic Acid Diethylamide), *A.M.A. Archives of Neurol. and Psychiat.*, 1958, 79, 201.)

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A STATISTICAL STUDY OF FACTORS INFLUENCING DISCHARGE FROM PSYCHIATRIC HOSPITALS

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ONE of the problems in psychiatric epidemiology is the use of hospital admissions for the study of true morbidity. Clearly this depends upon whether hospitalized cases can be regarded as a representative sample, in other words if admission to hospital varies from one social group to another, from one region to another, etc. Various authors have shown that the duration of hospital stay varies with social status, with marital condition, etc., and such variations in the chances of being *discharged* suggest similar variations in the probability of being *admitted*.

The duration of hospital stay has been examined for all first admissions to psychiatric hospitals in Norway, 1936-1945, a total of 16,038 cases. All these patients have been followed by means of a national registration system until the end of 1955, giving a minimum observation period of 10 years for patients not discharged at all. Patients re-admitted within 12 months are not considered discharged.

As expected *clinical diagnosis* is the decisive factor (Table I). Among the cases diagnosed as schizophrenia one-half are discharged within the first 12 months, while one-fifth stay in hospital for ten years or more. Patients suffering from functional psychoses of other types, mainly affective, will on the other hand rarely stay in hospital more than a year, and a mere 2 to 3 per cent. are left in hospital after ten years. Mental defectives and epileptics with psychotic complications show a discharge pattern very much like that of schizophrenia, while the remaining diagnostic groups, organic and symptomatic, tend to behave like the benignant functional psychoses. In the organic groups the high mortality complicates the picture: of the senile and arteriosclerotic patients one-half die during their first hospital stay, and for patients who stay in hospital for any length of time, the chances of being discharged alive are slight.

TABLE I

		Per 100 First Admissions								Died per 100 During First Hospital Stay	Re- admitted per 100 Dis- charged Alive
		Discharged Alive Within					Still in Hos- pital 1 Jan. 1956	Total			
		(whole years)									
		0-1	1-2	2-5	5-10	10-20					
		No. of First Ad- missions 1936-45									
Schizophrenia		5,646	50	12	11	6	4	17	100	9	39
Manic-depression		1,738	80	9	6	2	0	3	100	6	33
Other functional psychoses		3,069	79	8	6	3	1	3	100	4	26
Patients with mental deficiency		1,046	49	12	12	7	2	18	100	12	33
Patients with epilepsy		286	53	8	11	7	5	16	100	20	35
Senile and arteriosclerotic psychoses		1,641	72	12	10	3	1	2	100	48	15
General paresis		798	77	8	5	3	1	6	100	36	20
Other organic psychoses		364	78	6	5	4	2	5	100	30	20
Alcoholic psychoses		263	90	4	3	1	1	1	100	6	12
Other symptomatic psychoses		587	90	5	3	1	0	1	100	26	17
Other and unspecified psychoses		116	82	7	6	0	0	5	100	16	10
Non-psychotic		483	90	5	3	1	0	1	100	1	15
Total		16,038	66	10	8	5	2	9	100	14	30

TABLE II

Duration of Hospital Stay and Frequency of Re-admission for Major Diagnostic Groups by Sex, Marital Status, Result of First Hospital Treatment, Age on First Admission and Place of Residence. Group 5-20 includes Patients still in Hospital 1 January, 1956 as well as Patients Discharged After 5 to 20 Years. The Figures for "Results of Treatment" include only the Latter, however, and are Consequently Lower

	Sex		Marital Status			Result of Treatment	Age on First Admission						Place of Residence								
	Men	Women	Single	Married	Widowed		Divorced	Good	Fair	Poor	15-19	20-29	30-39	40-49	50-59	60-69	70-	Rural	Semi-urban	Minor Towns	Oslo-Bergen
Schizophrenia	0-1	..	..	..	..	..	80	52	51	60	57	47	46	41	39	66	48	51	54	50	53
	1-5	..	..	24	22	32	25	17	32	32	17	23	24	25	28	33	23	23	24	22	25
	5-20	..	..	28	22	26	37	3	16	17	23	20	29	29	31	28	29	26	22	28	22
	Re-admission	39	40	41	32	35	50	40	38	39	44	44	41	36	25	21	18	39	39	40	37
Other functional psychoses	0-1	..	..	76	84	78	55	85	78	71	81	85	82	81	73	75	74	79	81	82	80
	1-5	..	..	17	12	16	32	13	17	23	16	12	14	13	20	19	20	16	13	13	15
	5-20	..	..	7	4	9	6	2	5	6	3	3	4	6	7	6	6	5	6	5	5
	Re-admission	28	29	30	28	23	41	30	25	28	37	31	29	27	28	26	23	31	28	34	28
Psychosis with epilepsy and with mental deficiency	0-1	..	..	47	61	64	47	70	54	57	51	50	51	47	50	59	—	50	51	41	50
	1-5	..	..	24	22	14	18	24	32	29	27	24	18	22	29	19	—	24	20	39	19
	5-20	..	..	29	17	22	35	6	14	14	22	26	31	31	21	22	—	26	29	20	31
	Re-admission	32	36	34	37	9	33	37	35	31	40	38	31	28	29	28	—	33	31	36	36
Senile and other organic psychoses	0-1	..	..	70	79	74	63	84	80	74	—	72	78	77	76	68	77	67	69	73	65
	1-5	..	..	18	14	21	27	14	15	20	—	12	12	15	14	26	20	23	15	18	24
	5-20	..	..	12	7	5	10	2	5	6	—	16	10	8	10	6	3	10	16	9	11
	Re-admission	17	17	22	16	11	19	25	18	17	—	36	23	22	17	24	8	31	14	21	19
Others (mainly symptomatic psychoses and non-psychotics)	0-1	..	..	84	93	88	90	91	92	86	85	90	90	90	91	83	—	88	92	86	89
	1-5	..	..	12	5	10	6	8	6	12	15	9	8	6	6	14	—	8	6	12	9
	5-20	..	..	4	2	2	4	1	2	2	0	1	2	4	3	3	—	4	2	2	2
	Re-admission	16	15	18	12	12	21	15	13	16	21	16	17	15	10	13	—	14	14	18	19

The diagnostic differential is so marked that the diagnostic groups have to be kept apart during the statistical analysis of all other factors. In order to avoid splitting up the material too much, the number of groups is reduced from twelve to five in the following. Within each of these major diagnostic groups the discharge pattern is relatively uniform, and the sub-groups are closely related (such as senile and arteriosclerotic, general paresis and other organic psychoses).

Table II shows that the discharge pattern is very much the same in men and women. For schizophrenia early discharge is somewhat more common in the female sex (a difference of 4 ± 1.44 per cent.), whereas the opposite is the case for senile and arteriosclerotic psychoses. In order to simplify the tables the figures in the following represent both sexes.

The *result of treatment* is the only other factor with an influence upon the duration of hospital stay which is comparable to that of diagnosis. Actually these two correlate closely, because our diagnostic system is largely based upon outcome. In schizophrenia with a favourable outcome the discharge pattern is practically the same as in the more benign functional psychoses. Schizophrenic patients who are discharged as "unimproved" or as merely "improved", on the other hand, tend to stay much longer, and the same pattern is found for psychoses with epilepsy and with mental deficiency. In the remaining diagnostic groups, organic and symptomatic psychoses, the result of treatment is of little or no effect upon the duration of hospital stay, unimproved cases having the same discharge pattern as the much improved ones.

It may seem surprising that so many patients are discharged as unimproved after less than one year of hospital treatment. The explanation is that a certain improvement in social adjustment has been achieved, and that there is little hope for further improvement—so the patients and their relatives want to try a discharge, with or without the consent of the hospital. Furthermore a great number of these unfavourable cases are in Norway discharged to some other form of care, such as nursing homes or family care, and quite often this is done as soon as it becomes reasonably clear that the patient is unlikely to benefit from a prolonged stay. The overcrowding is a main reason for this practice.

It should be noted that the considerable number of patients who are still in hospital at the end of the observation period are not included in the figures, as they cannot be classified according to result of treatment. The overwhelming majority, however, belong in the unimproved category.

It is common experience that *married* patients tend to be discharged earlier than the single, but this is to a large extent a mere consequence of the difference in diagnostic distribution. Schizophrenia predominates in the single, while more benign forms tend to be more common in the married. But even when the diagnostic groups are considered separately the married have a significantly shorter hospital stay in all groups. This trend is equally marked in both sexes (not shown in table). The type and the closeness of social contact may make the return to an extramural existence easier for the married. It should not be overlooked, however, that within each of our coarse clinical groupings the married may tend towards more benign clinical pictures. This is certainly so for epileptics and mental defectives with psychotic complications, and it might easily be true even of the schizophrenics.

The *widowed* have a discharge pattern very much like that of the married, which seems to indicate initial selection by marriage rather than social contact as the decisive factor.

The *divorced* tend to stay in hospital even longer than the single. These patients, who were divorced previous to first admission and mostly previous to first onset of psychosis, are likely to have had particularly serious personality problems, and at the same time they have generally exhausted the tolerance and the resources of their relatives long ago.

Marital status is far from being a direct measure of the degree of social contact, as many single patients have lived in an equally close family relationship with parents and siblings. *Age on admission* may clarify this problem. Table II shows in fact that the younger schizophrenics, who are more likely to have parents who can take care of them, are discharged more rapidly than the older patients. This trend is not found in the other diagnostic groups, and on the whole age on admission does not seem to be a factor of great importance.

In previous investigations *social and economic status* has been found to play a role, in that high status correlates with early discharge and *vice versa*. To some extent this is a result of diagnostic distribution, as schizophrenia is relatively and absolutely more frequent in low status groups such as farm labourers and seamen. Age is another source of error, as low age on admission correlates on one hand with poor outcome (schizophrenia) and on the other hand with certain low status occupations.

When the discharge pattern is analysed for diagnosis and occupation the differentials are very moderate (Table III). A comparison of more or less parallel groups such as farmers and farm labourers does not show any consistent tendency for higher status to go with earlier discharge. Such a trend is

TABLE III

Duration of Hospital Stay by Occupation for the Three Main Diagnostic Groups. Men, and Married Women by Occupation of Husband. Also Re-admissions per 100 Discharged Alive

	Men				Married Women			
	0-1	1-5	5-20	Re-admission	0-1	1-5	5-20	Re-admission
Schizophrenia:								
Farm labourers	47	24	29	43	45	32	23	42
Farmers	47	17	36	35	45	32	23	36
Fishermen	47	17	36	36	57	22	21	19
Labourers	46	22	32	36	56	23	21	38
Artisans, technicians	49	27	24	39	51	26	23	39
Seamen, crew	40	31	29	37	59	14	27	39
Seamen, officers	55	18	27	21	75	19	6	20
Trade, employees	54	23	23	42	63	23	14	33
Trade, owners, managers	41	35	24	34	55	28	17	40
Public service	57	19	24	42	79	8	13	29
Professional service	56	20	24	36	60	9	21	54
Not gainfully employed	49	23	28	44	—	—	—	—
Other functional psychoses:								
Farm labourers	74	20	6	32	87	6	7	28
Farmers	77	19	6	21	82	15	3	39
Fishermen	79	17	4	34	80	13	7	28
Labourers	81	13	6	24	80	13	7	28
Artisans, technicians	83	12	5	31	85	13	2	26
Seamen, crew	77	18	5	41	87	5	8	32
Seamen, officers	88	12	—	12	80	10	10	7
Trade, employees	83	12	5	27	84	13	3	25
Trade, owners, managers	77	14	9	32	81	18	1	27
Public service	78	15	7	23	86	10	4	27
Professional service	88	10	2	30	81	14	5	27
Not gainfully employed	84	9	7	30	—	—	—	—
Senile and other organic psychoses:								
Farm labourers	64	15	21	25	81	13	6	11
Farmers	66	25	9	20	70	25	5	25
Fishermen	86	14	—	18	69	23	8	15
Labourers	79	15	6	16	84	14	2	14
Artisans, technicians	77	13	10	14	74	22	4	20
Seamen, crew	58	22	20	19	70	25	6	16
Seamen, officers	75	9	16	16	67	20	13	14
Trade, employees	77	14	9	14	68	28	4	14
Trade, owners, managers	80	16	4	15	82	10	8	11
Public service	85	7	8	20	73	23	4	14
Professional service	87	7	6	27	86	14	—	10
Not gainfully employed	72	—	28	15	—	—	—	—

found for seamen versus officers in the merchant marine, but for employees versus owners and managers in trade the trend is reversed.

Public service is a group of particular interest, in that the level of income is moderate, but with a high degree of security in case of illness. In this group the percentage of early discharges is high, particularly for schizophrenia, and definitely more for single women than for men and married women. This suggests that economic security rather than status may be decisive for the discharge of mental patients with a somewhat doubtful prognosis. When the prognosis is better and a full remission is to be expected, social security may on the other hand lead to a *prolongation* of the hospital stay in certain cases.

TABLE IV

Duration of Hospital Stay by Occupation for Three Main Diagnostic Groups. Single Women Gainfully Employed. Also Re-admissions per 100 Discharged Alive

			0-1	1-5	5-20	Re-admissions
Schizophrenia:						
Farm labourers	..	..	48	26	26	39
Domestic servants	..	..	50	26	24	42
Labourers	..	..	50	24	26	43
Artisans	..	..	55	23	22	35
Trade, employees	..	..	55	22	23	42
Public service	..	..	63	18	19	57
Professional service	..	..	56	22	22	34
Not gainfully employed	..	..	52	21	27	36
Other functional psychoses:						
Farm labourers	..	..	73	19	18	32
Domestic servants	..	..	70	21	9	33
Labourers	..	..	85	9	6	20
Artisans	..	..	76	20	4	37
Trade, employees	..	..	82	11	7	31
Public service	..	..	76	18	6	29
Professional service	..	..	67	20	13	35
Not gainfully employed	..	..	79	14	7	30
Organic psychoses:						
Farm labourers	..	..	57	26	17	26
Domestic servants	..	..	80	10	10	12
Labourers	..	..	76	20	4	14
Artisans	..	..	78	13	9	18
Trade, employees	..	..	66	25	9	19
Public service	..	..	72	28	—	36
Professional service	..	..	75	25	—	38
Not gainfully employed	..	..	57	23	10	24

Seamen are in many respects placed at the other pole with regard to social security, and in accordance with this we find very low percentages for early discharge. This is not so for seamen's wives, however, which is not surprising.

Patients not gainfully employed at the time of first admission (mostly young sons and daughters living with parents) do not differ much from the other groups. In diagnostic groups with a poor outlook (such as schizophrenia) early discharge is not particularly common, whereas in the more benign (affective) group there is a slight tendency for these patients to be discharged early. One might conclude that parents are not particularly anxious to receive sons and daughters who have been hospitalized for a psychosis, unless the outlook is comparatively favourable. In eight out of 12 occupational groups the

percentage of early discharges for schizophrenic patients is higher for married women than it is for "daughters".

On the whole we have been unable to confirm earlier findings from as different parts of the world as New England (U.S.A.) and Singapore that social class is of decisive importance for psychiatric treatment—at least not as far as the major psychoses go. In Norway the well-established nation-wide sick-insurance, the lack of private institutions for the insane, etc., will tend to level out all differentials in the standard of medical care as well as in the attitudes of patients, doctors and relatives.

Place of residence (Table II) does not have much influence upon the discharge pattern, not even when such extremes as typically rural districts are compared with the two major cities. The organic psychoses represent the only exception, with a significantly higher proportion of early discharges in the major cities. The main reason is that in Oslo a large number of senile and other organic psychoses are admitted to psychiatric receiving hospitals for examination and placement, while in other parts of the country such patients tend to go directly to nursing homes. etc.

Clearly discharge is a function not only of the patient but even of *the hospital*. Therapeutic efficiency and optimism, local conditions, discharge policy, etc., are bound to play a role. In Table V the ordinary mental hospitals of Norway are compared, hospitals with a selected clientele (such as the criminal insane) being excluded. The most definite trend is a geographical one. With two exceptions (both being old hospitals in poor repair) the hospitals along the southern and western coast and way up north have a shorter hospital stay than any of the hospitals in Eastern Norway. In the former group the percentages of patients discharged within one year range from 72 to 83, while in the Eastern hospitals the range is from 48 to 70. These western and northern mental hospitals have very little in common, some are old and some more modern, and they are not more overcrowded than the eastern ones. In the West and the North the incidence of mental disorders, as measured by the rates

TABLE V

Length of Hospital Stay (Whole Years) in Major Mental Hospitals, Men and Women, All Diagnoses, 1936-45

		0	1	2-4	5-9	10-	Total
Veum	Eastern including Oslo	63	13	14	5	5	100
Sanderud		63	12	13	5	7	100
Presteseter		48	19	16	8	9	100
Gaustad		55	13	14	9	9	100
Dikemark		70	13	10	4	3	100
Blakstad		66	12	11	6	5	100
Lier	South-eastern	69	9	9	6	7	100
Faret		76	8	6	5	5	100
Eg	Southern	60	14	15	7	4	100
Dale	South-western	73	9	9	5	4	100
Valen	Western including Bergen	72	13	9	3	3	100
Nevengården		74	10	11	3	2	100
Opdøl		72	11	9	5	3	100
Østmarka	Northern	83	7	5	3	2	100
Rotvoll		61	10	13	8	8	100
Rønvik		76	8	7	5	4	100

of first admissions, ranges from the highest in the country (Rogaland) to the lowest (Nordland and Troms). Economically Eastern Norway may on the whole be better off, and the population is generally supposed to be less frugal than the Westerners and Northerners, with a higher standard of living, particularly with regard to housing. This might paradoxically make them less tolerant of mentally abnormal relatives. The more advanced level of industrialization and urbanization may play a similar role. During the period of investigation two large and effective receiving hospitals existed in Oslo, and most of the admissions to them came from Eastern Norway, while similar clinics did not at the time exist in other parts of the country. It is common experience that such hospitals tend to receive a disproportionate number of benign cases, which leads to a lowering of the patient standard in the mental hospitals of the same district. In our statistical material these receiving hospitals are included, the only exception being Table V.

RE-ADMISSION

The tendency towards relapse is an important factor in the discharge pattern. As a simple measure of this tendency we have included in the tables the number of patients re-admitted per 100 discharged alive. As previously mentioned, patients re-admitted within 12 months of discharge have not been considered as discharged at all, which simplifies the statistical treatment of the many patients who go in and out of hospital with brief intervals.

TABLE VI

Re-admissions per 100 Discharged Alive by Length of Hospital Stay and by Condition on Discharge. The Durational Groups 5-10 and 10-20 are Pooled for the Four Lower Diagnostic Groups, because the Number of Cases is Small

			0-1	1-2	2-5	5-10	10-20	
Schizophrenia	..	..	Good	41	41	35	29	10
			Fair	44	43	35	21	16
			Poor	40	45	44	36	12
Other functional psychoses			Good	30	32	31		24
			Fair	23	38	42		12
			Poor	26	41	40		18
Psychoses with epilepsy and with mental deficiency			Good	42	36	27		6
			Fair	33	50	36		27
			Poor	30	36	36		22
Senile and other organic psychoses			Good	26	24	10		17
			Fair	16	25	27		19
			Poor	13	17	24		15
Others (mainly symptomatic psychoses and non- psychotics)			Good	14	15	27		20
			Fair	13	13	0		20
			Poor	14	41	21		20

One might expect a negative correlation between length of hospital stay and frequency of re-admissions, but no such trend is borne out by the statistical data (Table VI). The only possible exception is the small group of psychoses with epilepsy and with mental deficiency. For patients with this diagnosis who were discharged in good condition, the tendency towards relapse seems to be lower if they have stayed in hospital for more than one or two years. The difference is not statistically significant, however. In these cases therapy consists

mainly of habit training in the hospital regime, and it takes time for results to consolidate.

When the hospital stay is prolonged over years, the age factor enters into the picture, and this is most likely the reason why re-admission appears to be rare in schizophrenics and organics with more than ten years hospital stay. Also it should be pointed out that the observation period for discharged patients is shorter for patients with a prolonged hospital stay (in fact it may go down to zero for patients discharged just before 31 December, 1955), and consequently these patients are exposed to the risk of relapse during a somewhat shorter period of time.

In the non-schizophrenic functional group re-admission appears to be less common in patients with an early discharge, particularly when the condition on discharge was unsatisfactory. This somewhat paradoxical finding indicates that it may be useless or contra-indicated to prolong the hospital stay if the course of a presumably benign psychosis is less favourable than expected. (The relation of re-admissions to result of treatment will be discussed more thoroughly in another paper.)

On the whole there does not seem to be any general tendency for length of hospital stay to be related to frequency of re-admissions, and this makes it justifiable to look for more special correlations (Tables I-IV).

The percentage of re-admissions decreases markedly with *age*, particularly after the age of fifty, which is a natural consequence of the decreasing life expectancy. This represents a source of error whenever groups are being compared which differ in age, such as the single and the married. The influence upon the discharge pattern of *marital status* appears to be confirmed by the figures for re-admission. Not only do married patients tend to be discharged earlier, but they are also less commonly re-admitted. For schizophrenia the difference between 41 per cent. re-admissions for the single and 32 per cent. for the married is formally significant beyond doubt (9 ± 1.76 per cent.), but most likely this is due to the difference in age distribution, and so the hypothesis of a real difference in the discharge pattern does not find any definite support in the re-admission data. The divorced, on the other hand, have in addition to their low rate of early discharge a high rate of re-admission *in spite of their higher age*. This confirms the conclusion that divorced patients are less readily accepted outside the hospital than are the single and the married. This is so for all diagnostic groups.

The tendency towards re-admission is unrelated to *place of residence*, with one important exception: patients suffering from organic psychoses are more readily re-admitted if they come from rural districts, while re-admission is much less common in the large cities. This unexpected finding may mean that the cities have provided a more varied care for such nursing cases, which makes re-admission to psychiatric hospital unnecessary. The finding that early discharge of organic psychotics is much more common in the major cities, points in the same direction.

The general impression that *social and economic status* has little or no influence upon the discharge pattern, is confirmed by the re-admission data. There is no consistent tendency for low status to go with a high frequency of re-admission. Where such a trend seems to occur, it is readily explained as a result of difference in age distribution. The re-admission rate is 43 per cent. for schizophrenic farm labourers as against 35 for farmers. Similarly it is 42 for employees in trade and industry (mostly clerks) and only 34 for owners

and managers. But this corresponds roughly to the differences found between patients in their twenties and in their forties, and is therefore probably an artefact. Unfortunately the material is not sufficiently large for a study of age specific occupational groups.

Certain irregularities are hard to explain, such as the high percentage of re-admissions in farmers' wives suffering from non-schizophrenic psychoses: 39 per cent. as against 27 to 28 per cent. in most other occupational groups. Other irregularities are probably due to small numbers.

The high incidence of early discharge in the "socially secure" group of public servants is found to go with a high percentage of re-admissions, particularly in single women suffering from schizophrenia. Evidently social and economic security may lead to early discharge even in cases where it turns out to be medically unjustified.

Seamen have a moderate to high percentage of re-admissions, which is at least not inconsistent with their low percentage of early discharge and with the assumption that the discharge pattern of this group is influenced by social insecurity.

CONCLUSIONS

The chances of a mental patient being discharged from hospital is dependent upon numerous factors, the more important being clinical diagnosis and outcome of hospital treatment. The possibility of using the discharge pattern as a measure of the tendency of society to accept mental patients, and of the ability of such patients to adjust outside of hospital, has been examined, and certain meaningful results seem to confirm that this is a possible approach in social psychiatric research. The great number of interplaying factors make a somewhat detailed statistical analysis necessary, and even our material of 16,000 first admissions followed for twenty years proved to be insufficient for certain special purposes, such as the elimination of possible statistical errors due to differentials in age distribution.

The findings indicate that social conditions connected with marital and occupational status have a significant but moderate influence upon the discharge pattern. The married appear to be a favoured group in comparison with the single, while the divorced are definitely handicapped. When occupational groups are compared, the differences are much more moderate, and a clear and definite trend could not be established. Certain findings indicate a relation between social security during illness and early discharge, but this trend is much less marked than has been reported from other countries.

On the whole social conditions as expressed in statistical data on marital status, place of residence or occupation does not in Norway influence markedly the relations of mental patients to psychiatric hospitals. This may have something to do with the organization of medical care, and with the entire social structure. To some extent the more pronounced findings reported from other countries may, however, be due to a less detailed differentiation of the material. If diagnostic groups are not kept apart, one will for instance find a higher correlation between low social status and prolongation of hospital stay, because of the correlation between schizophrenia and low social status.

In conclusion, this statistical study of the discharge pattern has failed to reveal any very serious shortcomings of this particular type of hospital statistics. In the study of mental disorders in relation to such social factors

as residence, marital condition or occupational status, the *relative* morbidity rates which can be calculated from such hospital material should, therefore, give a fairly undistorted picture of corresponding relations in true morbidity.

SUMMARY

For 16,000 first admissions to psychiatric hospitals in Norway, 1936-45, the pattern of discharge and re-admission has been studied, with regard to such factors as clinical diagnosis, outcome, age on admission, place of residence, marital status and occupation. Certain moderate but significant and apparently meaningful findings are reported, which seem to show that the chances of social rehabilitation may differ somewhat from one social group to another. These differentials are much more modest, however, than those reported from other countries.

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TESTING FOR INTELLECTUAL IMPAIRMENT —SOME COMMENTS RECONSIDERED

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As Piercy (1959) has pointed out, it is generally agreed that currently available psychological tests for detecting brain damage (Yates, 1954; Meyer, 1957) or early dementia (Shapiro, 1952; Inglis, 1958) are by and large poorly standardized and poorly validated. If the clinical psychologist attempts such detection he can make very few positive statements if all he does is administer those standardized tests which even approximately meet the commonly accepted standards of validity.

We agree with Piercy when he points out that a basic weakness in most of these tests is that they are founded upon the probably incorrect assumption that brain damage produces only one kind of abnormality. It is, in fact, highly likely that different kinds of brain damage can impair a number of distinct functions. In other words, brain damage should not be regarded as producing some easily measurable change along a single dimension. It would indeed be surprising if lesions of different extent, in different areas and of different aetiology did not have quite different effects upon behaviour.

A study recently reported by Meyer (1959) indicates, for example, the importance and behavioural relevance of which side of the brain is damaged in the temporal region alone.

Like Piercy, we cannot agree with Yates (1954) that the construction of valid tests must await the development of some generally applicable theory of brain function. Should we wait this long for satisfactory indices of impairment little practical work would be done for decades, perhaps even centuries.

Few, then, would dispute the fact that, in this area at least, the clinical psychologist has hardly any acceptable, objective tools which can be used routinely. A question often hotly disputed, however, is what the clinical psychologist should then do when he is called in to deal with the problem of ascertaining impairment. Piercy suggests that the only thing that can be done is to allow the clinical psychologist to interpret his test results in the light of his own judgment and clinical experience. He argues that, "Human error must be tolerated if other sources of error are greater" (1959, p. 493), and that the psychologist with his experience of cognitive tests and dementing patients is the best person to make a decision in these cases.

He draws an analogy between this kind of judgment and that required of a good chess player. He reminds us that in the game of noughts and crosses, where the rules and combinations of play are few, it is possible to programme

a machine so that it will make the "perfect judgment" of each play. Chess, however, is so complex and the combinations of moves so many that the programming of an analogous machine is not practicable. Nevertheless good chess-players are able to weigh up sufficient alternatives to defeat players who mechanically, and with less foresight, follow a few of the formal rules of procedure.

This seems to be an exceedingly misleading analogy. In its use the many rules and relations of the chess game presumably correspond to the many parameters of brain function. It is then argued that no machine (or battery of tests) can in practice successfully examine all the combinations possible in a single game (or patient), although a good player (or clinical psychologist) can produce a better-than-chance prediction by a subjective assessment.

Unfortunately for both the analogy and the psychologist, unlike chess, where the rules are known and only the complexity of possible relations precludes a "mechanical" solution, in the case of brain damage the very rules of function and dysfunction are themselves unknown. The psychologist who makes a "subjective assessment" is therefore less like a good chess player who subtly comprehends a large complexity of known relations and more like an autocratic opponent who, without consultation, makes up his own private rules as he goes along. Such a player might soon put his opponent's King in check. We would not, however, necessarily agree that this is a satisfactory way of winning. Similarly, the "experienced clinician" can always appear to make valid judgments of impairment so long as the only criterion of their validity is the fact that he on the basis of his experience has uttered them. We would not necessarily agree that this is a satisfactory way of working.

However, even if all the facts *were* known, but were too numerous to collate for an individual case, there is some evidence that judgment in clinical psychology is not much like judgment in chess—even if we leave aside the fact that the stakes for which we play are incomparably higher. For example, in the well-known study by Kelly and Fiske (1951) it was shown that the overall judgment by clinical psychologists of a number of facts, some of which were individually valid predictors of a criterion, was not better than chance, although better than chance "mechanical" prediction from each of several simple facts (test results) was possible. Thus, there is some evidence against the notion that "the human brain is the best available instrument for assessing" (1959, p. 493) this kind of evidence.

Essentially, Piercy differs from other authors (Shapiro, 1951, 1957; Payne, 1953, 1957) concerning the kind of method the clinical psychologist should use; but this, in itself, rapidly decides what the clinical psychologist will come to be. Piercy believes that he should use his "clinical judgment" just as the doctor does. But it then becomes extremely difficult to distinguish between the functions of the psychologist and the psychiatrist or the psychologist and the neurologist; except, that is, for the fact that the psychologist commonly lacks the crucial training in physical medicine which the other specialists have had. He no longer has a unique contribution to make but tries to be a kind of pseudo-psychiatrist or neo-neurologist.

Not only does Piercy suggest that the psychologist should adopt part of the role of these others, he recommends the acceptance and use of their ideas and hypotheses. He argues that, "An alternative approach is to examine test results with respect to their degree of approximation to known syndromes of intellectual disability" (1959, p. 495). To whom, we may ask, are these syndromes "known"?

The objective psychological evidence for the existence of any easily identifiable "syndromes of disability" is slender indeed. How approximate, we may enquire, are we allowed to be in making guesses perhaps crucial to the patient's treatment and future welfare? Knowledge of the size of error of measurement alone which attaches to all psychological estimates should make us extremely wary of accepting the relevance of such vaguely defined approximations.

Surely it is better for the clinical psychologist to pursue his own independent objective line of enquiry which does not take psychiatric conceptions for granted. It would seem far more useful to be able to demonstrate a few indisputable facts about a patient and his dysfunctions rather than to accept without question some of the received ideas of psychiatry and try to apply them through tests.

In his paper Piercy makes a number of statements about the kind of estimates upon which the psychologist may base his judgment. A few examples may be quoted. Thus, "... on a test of rote verbal learning, one patient may be impaired as a result of a slight but strongly perseverative error whereas errors produced by another patient obtaining an identical score may be extremely variable. The distinction is not trivial since the latter is more typical of dysphasia and is thus of localizing value" (1959, p. 491).

"Again, if on this type of test (Kohs' blocks) the trial is discontinued as soon as the conventional time limit is exceeded, the opportunity to distinguish between depressive and organic intellectual impairment may well be lost" (1959, p. 492).

"... the interpretation placed on the ability to repeat 7 digits forwards and 5 backwards should be quite different from that placed on the ability to repeat only 5 digits forwards but 7 backwards" (1959, p. 492).

It would, to say the least, certainly seem desirable for the psychologist to investigate such statements as these before accepting them as procedural guides. It may be that such indicators can be recognized "from experience", but if a statement founded upon the psychologist's "experience" is to be given more weight than that of any other clinician who may choose to dispute it, then it must be a demonstrable, objective and repeatable fact.

Finally, two extremely general points must be made in regard to Piercy's contentions.

In the first place, he does not seem to recognize sufficiently clearly that the "problem of dementia" often presented to the psychologist usually contains within itself a number of different questions which *must* be considered separately. At least two kinds of questions can commonly be distinguished, these are:

1. *Descriptive*: (e.g.) (a) Is there any evidence of a *general* falling off from a previously higher level of ability?

- (b) Is there any evidence for some *specific* impairment such as amnesia, dysphasia or the like?

2. *Aetiological*: (e.g.). Is there any intracranial pathology or damage present?

Now, while we may agree with Piercy that most standard tests are of little use, this is partly because their constructors have similarly failed to recognize the different questions which go to make up the general problem. Once it is recognized what specific questions are being asked it is likely that more successful attempts may be made to answer them. One may, for example,

utilize available tests or make up new tests to *describe* specific abnormalities (viz. Inglis, 1957). It is important to emphasize that the psychologist should be capable of attempting the experimental description and analysis of any behavioural abnormality however "subtle" and "qualitative" this may seem at first sight to be. It is almost always possible to examine the significance of any apparent abnormality by comparing the patient's performance with that of a group of control subjects. Unless we do this we are bound to fall into the error of accepting as indicative of a specific disorder some apparent difficulties which even a brief investigation might show to be characteristic of at least some individuals who do not suffer from the disorder being investigated.

As regards the aetiology of disorder Piercy seems content to suppose that certain subjectively assessed descriptive characteristics must necessarily have causal implications. As Payne (1958) had previously pointed out, however, even if a test can be shown to have a certain number of valid descriptive implications it cannot simply be assumed that a limited set of aetiological implications follow. These latter implications must themselves be proven before the test results can be used to make inferences about causation. A similar argument may be put forward concerning prognosis. Valid descriptive characteristics are not necessarily valid prognostic indicators and the psychologist can and must tackle this problem in its own right.

The second general point is this. Throughout his paper Piercy is concerned to emphasize that while many "theoretical" objections can be raised against current practices in testing for deterioration the actual problem is a "practical" one and must be tackled with the means at our disposal. We, on the other hand, would argue that medicine has advanced not because the sciences upon which it is now founded have accepted its limitations, but because they have transcended them. The help that bacteriology has given to surgery was not produced by a more refined understanding of, or harder work based upon, the notion of "spontaneous generation" but came from an experimental approach to the problems of fermentation and infection. The principal contributions that the basic sciences have made to medical problems have often sprung from a refusal to plead the exigencies of "clinical pressure" or the urgency of "practical problems". Again and again in the history of medicine such pleading has been made the reason for continuing to do what has been done. Again and again the real problems have been outlined and solved by those who have refused to accept custom as a substitute for reason.

SUMMARY

A critical examination has been attempted of an argument recently restated by Piercy (1959) that a "flexible" approach is necessary to psychological testing in the clinic. It has been suggested that such an approach, far from being advantageous, tends to deprive the psychologist of his ability to add anything to psychiatric and neurological opinion since his contributions tend to be less the providing of evidence and more the imitation of procedures already carried out by the other specialists.

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A CONTROLLED TRIAL OF IPRONIAZID IN THE TREATMENT OF ENDOGENOUS DEPRESSION*

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INTRODUCTION

IN conducting drug trials nowadays one is aware of at least some of the difficulties that have to be faced and the possible traps lying ahead. It is probably true to say that perfection is unattainable in trials of this nature because of the unpredictability of the human material concerned—both the tested and the observers sharing this common fallibility. It is necessary to attempt so to arrange the experiment that the magnitude of the errors is kept to a minimum and the results remain unobscured.

One is very conscious of the placebo response and the papers of Hawkings and Tibbetts (1956) on acetylcholine and carbon dioxide therapy come to mind. Both these forms of treatment were found to give good results in 50–60 per cent. of cases—an encouraging finding which was equalled by the effects of the placebo. One recalls, too, the paper of Beecher (1955) who found that whilst morphia relieved post-operative pain in 75 per cent. of cases, 30 per cent. were equally well relieved by a placebo. There is little doubt that the placebo response has played some part in the results reported in this paper both among treated and control groups. Some of the therapeutic successes may have been the result of chance, for in a phasic and self-terminating illness such as endogenous depression the possibility of a spontaneous remission coinciding with the period of drug administration should not be overlooked.

The responses of placebo reactors generally favour the treatment being administered, as one would expect from the hopeful attitude necessarily implicit in the therapeutic situation. Some patients—those who develop apparent toxic effects when given placebo tablets—may be regarded as negative placebo reactors and it seems reasonable to suggest that some of the side-effects attributed to the active tablets may be of the same nature.

The double-blind technique is far from being an infallible answer to the problems of clinical trials simply because for one reason or another the blindness is rarely absolute. As Kennedy (1959) has pointed out, both nursing staff and the patients have expectations. If one depends on the nursing staff for objective

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assessments and on the patients for subjective evaluation, errors are liable to accumulate. In the trial described, all assessments have been made directly by the medical staff involved but naturally these in turn were largely influenced by the patients' statements and opinions, though objective evidence of change was apparent in most cases that improved under treatment. Matching of the groups of patients might have been desirable but was quite impracticable. The only feature that was matched was the diagnosis. It was hoped that by obtaining a sufficient number of cases and allocating them at random a sufficient balance in other respects would be achieved.

In this trial one has endeavoured to achieve an experimental design which would prove generally acceptable, though in one respect at any rate—as will later be pointed out—it fell short of the desirable standard. It is worth pointing out that the criticisms of many trials—of inadequate controls, lack of matching, of disclosures as to which patients are having active or control tablets—though valid for “drugs of small effect”, lose much of their importance should the drug be a really effective agent. With substances as dramatic in their action as penicillin, controls are virtually superfluous. Doubtless, “drugs of small effect” are of interest pharmacologically and as a possible indication of future developments, but in practical therapeutics they are of little importance. Consequently one felt that though it was essential to conform to the tradition of the double-blind technique, one would feel that the drug tested was not likely to be of much value if one was unable—in spite of all precautions—to be able to predict which patients were likely to be on the active and which on the inactive tablets. The occurrence of side-effects is a very suggestive clue, but may prove misleading.

Iproniazid was synthesized in 1951 and introduced a year later as a possible successor to isoniazid in the treatment of tuberculosis. It was noted that the patients treated showed an improvement in their clinical condition out of proportion to the changes in their X-ray appearances or to the improvement in their bacteriological findings (Cheifetz *et al.*, 1954). Their appetites became voracious and they showed marked gains in weight. A few patients, being given much larger doses than is now customary (of the order of 300 mg. daily), developed psychoses described as being of a euphoric type (Bosworth, 1956).

It was found that iproniazid was a strong monoamine oxidase inhibitor and a weaker inhibitor of diamine oxidase (Zeller *et al.*, 1954) and that its administration led to a rise in the brain serotonin level (Bogdanski *et al.*, 1956). It was also noted that it reversed the usual effect of reserpine in rabbits, giving rise to excitement. Saunders and his co-workers (1959) were impressed by these various findings and felt “that it might have some effect upon depressed, withdrawn patients, regardless of diagnostic category, in contrast to hyperactive, agitated assaultive patients in whom reserpine and the phenothiazine derivatives act most effectively”. The patients treated were, in fact, long-standing withdrawn schizophrenics. A favourable response was reported in 63 per cent., though only one patient was discharged from hospital. With this encouragement the drug was tried on depressives. It was found that three out of four depressives did well, if not better than with E.C.T., when given 150 mg. daily until a therapeutic effect had been obtained, followed by a maintenance dose of 10–25 mg. daily.

Further reports of the effect of iproniazid in depression have appeared. Furst (1958) obtained a good response in 75 per cent. of 100 cases of depression and de Verteuil and Lehmann (1958) reported the effects of iproniazid on 31

cases in which depression was a prominent symptom. Eleven showed a significant improvement but 4 of these relapsed. A high incidence of side-effects was noted and there was one death from liver necrosis. In most cases the dose employed was 150 mg. of iproniazid daily. The authors felt that it was an effective agent in treating depression but that the side-effects were sufficiently serious to discourage its further use—at any rate by them. Settel (1958) found that 70 per cent. of 48 elderly depressed patients did well. Robie (1958) claimed that improvement or recovery occurred in 78 of 100 cases of various types of mental illness, mostly depressives. None of these trials was controlled. In this country little has as yet been published on the use of iproniazid in depression. In June, 1958 Dally reported his experiences with the drug. Ninety-nine depressives were treated and of these 15 recovered, 23 were improved and the others either remained unchanged or became worse. There was a very marked correlation between weight loss during the illness and improvement on the drug. Dally appeared to find the drug most useful in cases of long-standing mild depression belonging to both the manic depressive and involuntional groups and noted that it was of little value in severe depression, particularly if agitation were prominent.

METHODS

The trial of iproniazid was carried out on patients admitted to the In-patient Unit of the Department of Psychological Medicine at the Newcastle General Hospital and to St. Nicholas' Hospital, suffering from endogenous or involuntional depression. Doubtful cases—those in whom reactive elements were prominent and those in whom there were grounds for suspecting paraphrenia—were excluded, as also were a number of the more severe cases whose clinical condition was such that one could scarcely justify the risk of three weeks' ineffective treatment. The cases were allocated in strict rotation to one of three groups—iproniazid A, iproniazid B and E.C.T. In fact, iproniazid A was the active agent and B the placebo, but this was unknown to all those concerned with the trial though the truth was long suspected. It would have been better had we not known to which of the groups each patient belonged but administration of the trial was carried out entirely within the Department and it was difficult to avoid.

The purpose of the trial was to decide whether iproniazid was effective in cases of endogenous depression and, secondly, to compare its effects with those of E.C.T. The iproniazid and placebo tablets were given for a minimum period of three weeks. A standard dose of 50 mg. t.d.s. was given throughout this period. It may be that a smaller dose would have been sufficient but it seemed undesirable to introduce the possibility that failure of treatment might be due to inadequate medication. It also appeared that this quantity was the largest that could be given with a reasonable chance of avoiding serious side-effects. It is possible, too, that the period of three weeks that was chosen might with some slight advantage have been longer. However, subsequent experience showed that most cases manifesting a response began to improve within this period and we felt that in view of the fact that some other form of treatment might have to be initiated after the period of the trial, necessitating further detention in hospital, that humanitarian and economic factors had to be taken into consideration. If there was inadequate improvement in the patient's condition after this period, E.C.T. was given. No other drugs were permitted, apart from nightly sedatives, mild analgesics and laxatives when indicated.

Those patients allocated to the E.C.T. group were given the optimum number of convulsions for their condition and no attempts were made to standardize the treatment.

Altogether 81 patients have taken part in the trial. Of these, 26 received iproniazid, 28 the placebo, and E.C.T. was given to 27. Of those given iproniazid 15 were female and 11 male; the placebo was given to 17 females and 11 males, whilst 20 females and 7 males were treated by E.C.T. The imbalance between the sexes is partly due to the fact that of the 30 cases from St. Nicholas' Hospital, 27 were drawn from the female side of the hospital. The average age of the iproniazid group was 54 years, of the placebo group 52 years and of the E.C.T. group 55 years. In each case the patient's clinical condition was assessed weekly and in those treated with tablets, if no improvement occurred, the final assessment was made after three weeks. In those in whom significant improvement had occurred, it was usually possible to make the assessment after three to four weeks but an occasional patient continued to improve after this time, though it was never necessary to delay the final assessment later than six weeks after commencing treatment. In the E.C.T. group, assessment was made 7-10 days after the last treatment had been given, when the confusion engendered had entirely or largely disappeared.

All the cases are being followed up and further assessments are being made at three and six months after the commencement of the treatment. The results of this follow up study will be reported later.

The clinical condition of each patient was rated as worse, unchanged, slightly improved, greatly improved or symptom-free. For the purposes of the trial results, the first three categories (worse, unchanged and slightly improved) have been amalgamated as a not worthwhile or poor result, whilst the latter two categories (greatly improved and symptom-free) have been incorporated as a worthwhile or good result. Such patients were able to leave hospital and carry on a normal life without undue effort. We do not feel that minor degrees of improvement are worth considering in evaluating the influence of iproniazid on depression as we already have a highly efficient form of treatment for this condition in E.C.T.

RESULTS

The results so far obtained are as follows (see Table I). Of the 26 patients given iproniazid, 14 showed worthwhile improvement and 12 did not. On the placebo, 3 patients showed a worthwhile result and 25 failed to respond. On E.C.T., the figures were 24 and 3 respectively. The improvement in the iproniazid group began 4 to 24 days after administration, the mean being 9-10 days. The superiority of iproniazid over the placebo which is apparent from the above figures is a highly significant finding and with Yates' correction for small groups, $p < 0.01$.

TABLE I

	Good Result			Poor Result	Totals
Iproniazid	..	..	..	14	12
Placebo	..	..	..	3	25
E.C.T.	..	..	..	24	3
					26
					28
					27

There is no correlation between improvement or failure and age, elderly patients doing as well as those in younger age groups. As far as sex is concerned, 7 out of 14 females did well on iproniazid and 7 out of 12 males.

Although these figures are too small to be of great significance they lend no support to the suggestion that there is a sex differentiation in the response to iproniazid.

The low response to the placebo is striking in comparison with the well-known placebo response of other groups of patients. It seems likely that this is due to the fact that the patients in this trial suffered from endogenous psychoses and were far less liable to the effects of suggestion than those, say, who featured in Tibbetts' and Hawkings' two trials.

SIDE-EFFECTS

As far as the patients on the trial are concerned, the side-effects so far seen have been trivial and in no case was it necessary to stop the administration of the drug. Of the 26 on iproniazid, 12 complained of effects which were likely to be due to its administration—though not necessarily to the actual drug itself. The most common complaints were a dry mouth, dizziness of a postural kind and constipation. Difficulty in initiating micturition occurred in four patients and diarrhoea in one. There was no suggestion of peripheral neuritis in any patient and no one developed jaundice. No pyridoxine or other vitamins were given. As far as jaundice is concerned, of something like 200 patients attending the Department who have been treated with iproniazid, two have developed jaundice—both fortunately recovering. One of these was known to have an enlarged spleen before being put on the drug. She was fully investigated and no cause was found for this. She developed jaundice after ten days on iproniazid.

One patient whilst on iproniazid, a man of 73, had a brisk haematemesis and melaena for which no cause could be found. It was not thought likely that it was related to the iproniazid, which was continued after a break of three days without further harm. One patient, having recovered from his depressive symptoms after a period of four weeks, became mildly hypomanic. This was realized only retrospectively when the patient and his wife declared that never before had he been so energetic and active. It appears that he returned home from hospital to carry out all the odd jobs in the house that had accumulated during the two years of his depressive illness. His energies returned to their pre-morbid level after three weeks when the dosage of iproniazid was reduced.

Six patients on placebo tablets complained of minor side-effects, notably drowsiness, dryness of the mouth, dizziness and nausea.

CONCLUSIONS

One can conclude from the results given above that iproniazid is an effective agent in the treatment of depression, though as far as the immediate results are concerned it is not as efficacious as E.C.T. However, the immediate effect is perhaps not as important as the result assessed after three or six months. This is the period in which most relapses after E.C.T. occur and it may be that the relapse rate after iproniazid is less, so that the final results are more equitable. Although the most severe cases were excluded from the trial, many of the patients treated could be regarded as severely depressed, a number of them showing quite marked agitation. These appeared just as likely to respond to iproniazid as the less severe forms.

SUMMARY

In a controlled trial carried out to evaluate the effect of iproniazid on endogenous depression the drug was shown to have a beneficial effect on 54 per

cent. of the cases treated. This result was intermediate between the effects of a placebo, on which 11 per cent. of cases improved, and E.C.T., as a result of which 89 per cent. achieved a good result.

ACKNOWLEDGMENTS

We are grateful to Roche Products Ltd., for supplies both of iproniazid (Marsilid) and placebo tablets. We should like to express our thanks to Professor Martin Roth for his encouragement and help and to Mr. R. Garside, Senior Lecturer in Psychology, who gave statistical advice on our results.

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Reviews

Biochemistry of the Central Nervous System. Edited by F. BRÜCKE. (Proceedings of the Fourth International Congress of Biochemistry.) Pergamon Press, London, 1959. Pp. 324. Price 88s.

This book is the published account of a symposium on the biochemistry of the central nervous system held during the 4th International Congress of Biochemistry in Vienna in 1958. It contains a great deal of useful information written by prominent workers in the field though the difficulty of presenting individual reports of a rapidly expanding subject between two covers is emphasized, in this instance, by haphazard presentation.

One of the striking things about modern neurochemistry is the way in which problems, seemingly intractable only a few years ago, are being successfully tackled. The metabolism of the galactolipids is a case in point. Not so very long ago our knowledge of the metabolism of cerebrosides seemed to have progressed very little since their discovery in the last century. In his article in this book Burton discusses a great deal of new work on the subject and suggests that the metabolic problems posed by the more complex gangliosides will be solved in the next few years.

Today every pharmacologist working on the nervous system will be familiar with γ -aminobutyric acid (or its monstrous abbreviation GABA); ten years ago this amino acid was only known as an interesting spot on a paper chromatogram. Roberts, one of the first to discover its high concentration in the central nervous system, has contributed an interesting account of its metabolic relationships in brain, whilst Elliott discusses its role in normal physiological activity as a likely inhibitory factor in nervous transmission. The importance of basic biochemical studies in understanding nervous activity is once more underlined.

A great deal of useful information about the metabolic activity of brain tissue has been obtained from studies of tissue fragments *in vitro*. McIlwain contributes a useful summary of the conditions necessary for the restoration and maintenance of the composition of cerebral tissues after removal from the body, whilst Quastel, with the benefit of half a lifetime of investigation of the effect of drugs on cerebral metabolism, discusses the effects of neurotropic drugs on enzymic mechanisms. He indicates that a rationalization of drug action will only come about as a sequel to a more complete knowledge of the metabolism of the nerve cell, a sentiment that will be sympathetically echoed by many investigators. At an even more fundamental level, problems of ionic movement in the nervous system are discussed at some length in the contributions by Ussing, Keynes and Nachmansohn.

In a challenging contribution Hydén describes work carried out on isolated glial and nerve cells. The statement "To dissect out ten Deiter's nerve cells and free them from adhering glial cells takes at present around five minutes" alone testifies to the diligence of his school of workers. He also puts forward the interesting proposal that there is an intracellular mechanism behind the engram based on the nucleic acids.

Mention has been made of the new investigations on cerebrosides but it is apparent that even the better established compounds of the brain, such as phospholipids, present their enigmas. Klenk makes pertinent remarks about the composition of phospholipids and in particular the complex fatty acid pattern, the significance of which is unknown. The biochemistry of the inositol phospholipids, ably considered by Folch-Pi and LeBaron, is even more involved. In fact nothing definite is known about the function of the phospholipids although they account for 20-25 per cent. of the dry weight of brain tissue. One of the great frustrations in the study of these compounds until recently has been the difficulty in separating component lipids. The analytical problems presented by the cerebral proteins are still greater which explains why Richter, in his review on protein metabolism, confines his discussion to the proteins as a whole.

The topics covered by this symposium are even more varied than is indicated in this review. Glutamic acid, serotonin and the catecholamines are all discussed by eminent scientists; there is, in addition, a lengthy summary of all the papers by the editor.

It seems a little curious that a paper on catecholamines should be sandwiched between papers on proteins and gangliosides whilst one on mucopolysaccharides is slipped in between two on serotonin. More unforgivable in a book of this type is the absence of an index, this omission is even more irritating in view of the high price asked by the publishers.

G. B. ANSELL.

Time Distortion in Hypnosis. By LINN F. COOPER and MILTON H. ERICKSON.

Cooper and Erickson have written a small book describing a phenomenon known as time distortion; a technique to produce it artificially in the hypnotic state, and the possibility of using this technique in various ways including psychotherapy.

Everyone is familiar with the way in which the appreciation of the passage of time can be altered by the state of mind of the person trying to estimate this passage: the slowness of an hour spent in boredom and the lightning passage of the same hour when we are absorbed is common knowledge.

The authors claim that they can train suitable hypnotic subjects to experience and demonstrate this distortion at will. This is done by training the subjects to live through a certain experience in a space of time which the subject imagines to be say 10 minutes and which actually is 10 seconds. There are various complicated techniques described in the book for achieving this end. Having described this method of compressing time, the authors then attempt to demonstrate certain uses of what they have obtained such as the increased ability to learn—both in motor and non-motor activities.

The authors also assert that there is evidence that with their technique the recovery of unconscious material is facilitated. They do *not* find that motor learning or mathematical mental activity is facilitated. The evidence for the authors' opinion is however pretty thin and based on a few experiments without adequate controls, e.g. their conclusions on non-motor learning are based on work with one subject.

Erickson, at the end of the book, describes the use of this technique in half a dozen psychotherapeutic cases. Again, a small series and no controls leave the conclusions very much in doubt. One is a little surprised also to see Erickson falling into the trap of attaching great importance to the unconscious material recovered by the use of this technique and attributing "cure" by catharsis. It is sad to see that a psychiatrist with such insight into defence mechanisms still ranges himself on the side of the naïve and untutored who attach such importance to the "lost memories" and not the repressing forces.

The overall impression that their book gives is of two talented research workers spending much time and energy on a trivial and inconclusive experiment, and having done so, have need to justify this expenditure of time by stretching the value of the experiment much beyond its true one.

T. F. MAIN.

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Potentiating Effect of Alcohol on Tranquillizers and Other Central Depressants

Extinction of a learned response under shock-avoidance conditions involving a two-choice discrimination situation was studied in rats.

In a newly-designed apparatus they have measured anxiety reduction, discrimination loss,

and inability to respond, as operationally defined. Phenaglycodol, meprobamate, and alcohol decreased anxiety and discrimination and increased the inability to respond. When the drugs were combined with alcohol, however, anxiety was potentiatingly reduced by meprobamate, chlorpromazine, and pentobarbital. Loss of discrimination by alcohol was potentiated by meprobamate, chlorpromazine, phenaglycodol, and pentobarbital. The complete inability to respond as induced by alcohol was also potentiated by meprobamate, phenaglycodol, and chlorpromazine.

(Authors' Abstr.)

Evaluation of Certain Drugs in Geriatric Patient

No statistically significant differences in beneficial effects were demonstrated when the changes induced by chlorpromazine, reserpine, or pentylenetetrazol were compared with effects of a placebo in senile female patients studied at the Rochester State Hospital.

In isolated instances of drug therapy, sustained improvement was observed to a degree not seen in the group of patients receiving a placebo. These isolated cases were fairly evenly distributed among the groups receiving the drugs under study. An initial improvement during the first six weeks of drug therapy observed in eight patients was followed by a regression to control levels when drug therapy was continued for an additional six weeks. Therefore, initial favourable responses must be viewed with caution.

Patients with the least degree of organic damage seemed to respond better than patients with advanced deterioration. However, the number of patients showing evidence of mild deterioration was small. A tendency to lower the level of functioning in many patients was observed with each of the medications, as compared with spontaneous deterioration observed in the group given a placebo. This tendency was statistically significant in the patients who received chlorpromazine, while the trend was not statistically significant for patients treated with reserpine or pentylenetetrazol.

Undesirable side-effects were most prevalent in the patients who received chlorpromazine. The side-effects included inertia, skin reactions, jaundice (in one case), and pallor. The most frequent side-effects encountered with reserpine included inertia, dryness of the mouth, and diarrhoea. Convulsions occurred in two patients and myoclonus in two patients who received pentylenetetrazol.

In general, it may be concluded that the use of chlorpromazine, reserpine, and pentylenetetrazol (Metrazol) will not effect any significant improvement in the groups of senile patients found in state hospitals.

Urinary "Epinephrines" in Patients with Mental and Emotional Disorders

Studies on the urines of patients with a variety of psychiatric disorders revealed increased excretion of urinary "epinephrines", i.e. epinephrines and/or substances related to it, in most of them. The range of values was the same in the various diagnostic categories and was not influenced by administration as such of tranquillizing drugs. However, improvement, by whatever means effected, was accompanied by lowered excretions.

The urines of depressed and/or psychotic patients contained an unstable fraction that had properties similar to those of adrenolutin: Reaction of this fraction with 2,3-naphthalenediamine yielded a compound with an absorption spectrum similar to that of the compound formed in the reaction between pure adrenolutin and 2,3-naphthalenediamine. Available evidence indicates that the urines studied contained a mixture of epinephrine and an adrenolutin-like substance. Since the latter substance constituted much or most of the urinary "epinephrines" excreted by psychotic patients, it appears that the quantity of catecholamines excreted by psychotic patients is much less than that by patients with anxiety neurosis.

The possible significance of these findings in interpreting the origin of certain mental symptoms is discussed.

(Authors' Abstr.)

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Parents of Schizophrenics, Neurotics and Normals

This study has concerned itself with testing the hypothesis that the degree of personality pathology manifested by a patient is a function of the degree of pathology characterizing his parents. The parents of 20 normal men, 20 neurotic men, and 20 schizophrenic men were compared with one another by means of a battery of techniques which included measures not only of individual functioning but also of spouse interaction patterns. It was found that parents of normal men are individually less maladjusted than parents of neurotics and parents of schizophrenics.

There were no apparent differences in this respect between parents of neurotics and parents of schizophrenics. It was further shown that both parents of normals and parents of neurotics may be distinguished from parents of schizophrenics by having closer, more harmoniously intercommunicating spouse relationships.

(Authors' Abstr.)

Disappearance Rates of Infused Epinephrine and Norepinephrine from Plasma

Increased adrenal-medullary and sympathetic-nerve secretions were simulated in a group of schizophrenic subjects and normal volunteers by means of intravenous infusions of epinephrine and norepinephrine. A study of the plasma concentrations attained by the infused catecholamines demonstrated that the rates of utilization of circulating epinephrine and norepinephrine were equivalent for the two groups.

(Authors' Abstr.)

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Production of High-Energy Phosphate Bonds in Schizophrenia

The levels of adenosinetriphosphate (ATP), adenosinediphosphate (ADP), adenylic acid (AMP), and fructose-1,6-di-phosphate (F1,6P) and the specific activities (radioactivity per minute per milligram) of ATP, ADP, and F1,6P were measured in the erythrocytes of 10 control subjects and of 10 acute and 10 chronic schizophrenic patients. These determinations were made under basal conditions and after 10 units of intramuscular insulin in a controlled setting.

Comparisons of mean levels of the substances mentioned above revealed no significant differences among any pairs of means, except that the AMP level of chronic schizophrenic patients under basal conditions was significantly lower than that of the control subjects.

Under basal conditions the ATP specific activity of chronic patients was significantly higher than that of the control subjects and acute patients. The ADP specific activity of the chronic schizophrenic group was also higher than that of the other two groups.

Insulin stress increased the specific activity of ATP in the control and acute schizophrenic groups, but decreased it significantly in the chronic patient group. The response to insulin of the chronic schizophrenic group was significantly different from that of the other two groups. The changes in ADP specific activity mirrored the changes in ATP.

Under basal conditions the F1,6P specific activity was significantly lower in the control subjects than in either schizophrenic group. The acute and chronic groups did not differ. Thus, this was the single measure which differentiated schizophrenic from non-schizophrenic subjects. Under insulin stress there was an increase in F1,6P specific activity for the control subjects and a decrease for both schizophrenic groups. These differences in response to insulin were significant.

All the substances measured are involved in biologic energy-transfer systems. Various alternative hypotheses were presented in explanation of the findings. The most likely hypothesis is that in schizophrenia there is a disturbance in the regulation of biologic energy formation and utilization. Further studies are in process to substantiate this evidence and to clarify a pathophysiological mechanism of schizophrenia.

(Authors' Abstr.)

Effect of Repeated Doses of Insulin on Excretion of Pyrocatecholamines

In summary, it has been demonstrated in mental patients undergoing therapy that repeated administration of insulin results in a markedly diminished response to this hormone, as measured by the output of epinephrine in the urine.

(Authors' Abstr.)

Acquired and Crossed Tolerance to Mescaline, LSD-25 and BOL-148.

It was possible to prove that tolerance to lysergic acid diethylamide (LSD-25) develops very rapidly in man. Tolerance to mescaline also occurs but less rapidly. Subjects tolerant to LSD-25 are very resistant to mescaline effects. Tolerance to mescaline, likewise, seems to be related to a certain resistance to LSD-25 effects. Prolonged administration of 2-bromo-d-lysergic acid diethylamide (BOL-148) does not cause the subject to be resistant to LSD-25. Tachyphylaxis effects to LSD-25 are not visible in man.

(Authors' Abstr.)

The Protein Metabolism in Anorexia Nervosa

A case of anorexia nervosa has been studied for 112 days, with particular reference to the protein metabolism. It is found that administration of large quantities of carbohydrate (61-70 Cal/kg. of body weight) sufficed to reduce the protein loss to a minimum of 0.025 gm. N per kilogram, i.e. 0.16 gm. of protein per kilogram.

In this case, a positive nitrogen balance was obtained, with ingestion of 0.31 gm. of protein per kilogram, or 0.05 gm. N per kilogram, with a caloric intake of 40 Cal/kg.

During the periods of starvation, the nitrogen excretion is found to be considerably greater, amounting to 0.18 gm. N per kilogram, i.e. 1.1 gm. of protein per kilogram of body weight.

The patient had a subnormal temperature and considerably decreased basal metabolism.

The importance is stressed of providing nourishment that is as adequate as possible in anorexia nervosa. Protein deficiency is best prevented by administration of large quantities of carbohydrate, as well as the largest possible amount of adequate protein.

(Authors' Abstr.)

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The Physiological Basis of the Treatment of Delirium Tremens

The current study involved the analysis of 700 cases of D.T., including a review of the causes of death of the 17 patients who succumbed to this illness. Forty-five patients were subjected to a study of their water and electrolyte disturbance.

Delirium tremens was found to be a combination of a physiological disturbance and an emotional stress in an individual whose relation to reality is, at best, tenuous. The particular mental event precipitating delirium was felt to be the "pharmacothymic crisis". The physiological disturbance was found to be varied and consisting of one or more of the following syndromes: (1) Dehydration; (2) Low serum magnesium; (3) Low salt syndrome; (4) Brain swelling. The last two, as well as the lack of resistance to infection, frequently found in delirium tremens, were assumed to be due to an inability to respond to stress. Owing mainly to a chronic vitamin deficiency, the alcoholic is unable to respond with the formation of desoxycorticosterone-like, prothogistic mineral-corticoids.

Methods of clinical diagnosis of the several physiological disturbances involved in delirium tremens were discussed, and suggestions were made to revise the management of this syndrome accordingly.

(Author's Abstr.)

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The Administration of BAS, 5-HTP, and Marsilid to Schizophrenic Patients

The administration to 5 chronic schizophrenic patients of BAS alone, of BAS and 5-HTP combined, and of BAS and 5-HTP in conjunction with Marsilid was not therapeutically useful. The fact that the patients did not react to the presumed increase in brain serotonin casts doubt upon the hypothesis that too little or too much serotonin is causally related to schizophrenia.

BAS appears to be a monoamine oxidase inhibitor. The conversion of 5-HTP to 5-HIAA was thus prevented resulting in an accumulation of serotonin in urine.

(Authors' Abstr.)

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Serum Toxicity in Various Psychiatric Disorders

The serum of schizophrenic, alcoholic, and mongoloid patients had no inhibiting effect on the respiratory activity of surviving rat brain. The serum of patients treated with chlorpromazine enhanced the respiratory activity. A slight tendency to elevated values found in recently admitted schizophrenic adults who were not taking chlorpromazine may be due to prior medication before admission. Phenylketonuric serum depressed brain oxidations, though a similar effect was induced by racemic phenylalanine in concentrations above 40 mg. per cent. as well as by other essential amino acids. It has been suggested that the depressant action of various amino acids may be due not to a direct effect of the amino acids, but to aldehyde formation. It has also been known for a long time that a number of toxic amines such as tyramine, phenylethylamine, mescaline, indole and skatol, all inhibit brain oxidations.

The observed phenomenon may explain the general depression of brain oxidations found *in vivo* in phenylketonuria by Himwich and Fazekas. The low cerebral metabolic rate found in mongoloid children *in vivo* by these authors may be due to the brain pathology associated with the condition.

(Author's Abstr.)

Clinical Findings in the Use of Tofranil in Depressive and Other Psychiatric States

1. Preliminary observation would indicate that Tofranil is a useful drug in the treatment of depressive states. It is not a tranquillizer and, therefore, is of little value in other conditions. It is a promising drug which can be used as an anti-depressant. However, its indication and scope must be studied for a longer period to determine what symptoms respond best to it.

2. The effect of Tofranil in many patients can be increased by the concomitant use of a tranquillizer or a stimulant. In a number of patients Tofranil, by removing the depressive elements, frees and exaggerates anxiety.

3. It can be used in combination with electric shock or after electric shock as a maintenance dose.

4. It is of little value in the treatment of schizophrenics and in paranoid types may often aggravate the condition and break down an unstable equilibrium to which the patient has become adjusted.

5. The combined use of Tofranil and a tranquillizer is helpful in certain psychoneurotic states, associated with anxiety or with reactive depressions.

6. It is of value in the treatment of depressions occurring in the older age group.

7. High doses are unnecessary and the effective range is somewhere between 75 and 150 mg. per day.

8. For the most part, side-effects are minimal, particularly in the younger age group. As one approaches the older age group, the frequency of such side-effects increases, but usually they are more uncomfortable than serious. In patients over 60 there may be a tendency to sudden falls which occur without warning. It is recommended that in older patients the dosage be limited to 75 mg. or less.

9. Side-effects can usually be reduced in frequency or intensity by a reduction in the dosage.

10. Long-term use of the drug is apparently necessary as patients may relapse, at least in the early stages when the drug is prematurely removed. Since the drug is rapidly excreted, it is necessary to give the medication 3 times a day.

(Author's Abstr.)

Sensory Deprivation and Schizophrenia; Some Clinical and Theoretical Similarities

It would seem, in fact, that they now have an experimental model of the schizophrenic syndrome superior to the "model psychoses" induced with mescaline or LSD. Not only will perceptual interference reproduce more closely the primary symptoms of schizophrenia, but these disturbances are caused entirely by external manipulation, without the confusion of a toxic psychosis. While of course they cannot assume that approaches such as these will give them valid answers to all their questions, the author believes they have here an important instrument to help them bridge the gap between the laboratory and the clinic.

(Author's Abstr.)

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Multiple Sclerosis as an Incidental Complication of a Disorder of Lipid Metabolism: I. Close Resemblance of the Lesions Resulting from Fat Embolism to the Plaques of Multiple Sclerosis

The first phase of this trilogy of studies on the possible genesis of the lesions of multiple sclerosis in a disorder of lipid metabolism is concerned with a case of delayed death incident to fat embolism of the brain. In addition to the expected widespread petechial haemorrhages, there were also found multiple, irregular foci of demyelination and focal necrosis whose gross appearance and distribution were quite reminiscent of the lesions of multiple sclerosis. To further strengthen this impression were the characteristic changes in the foci of demyelination as observed in the microscopic preparations. All of these lesions were apparently the result of lodgment of globules of fat in the small arterioles and capillaries of the white matter of the brain. The total picture presented by these lesions suggested the possibility that the lesions of multiple sclerosis might also be the result of the deposition in the brain of some lipid globules freely circulating in the blood stream. By the lodging of these lipid particles in the small blood vessels of the central nervous system, a clinical picture of this disease could thereby be produced. Additional studies on this point will point out contributing evidence which may lend support to this conception.

(Author's Abstr.)

Multiple Sclerosis as an Incidental Complication of a Disorder of Lipid Metabolism: II. A Survey of the Geographical, Clinical and Biochemical Evidence: The Significance of Endogenous Fat Embolism

In the first of the three papers of this series concerned with the possible aetiology of multiple sclerosis in some disturbance of lipid metabolism, the structural changes in the brain in a case of delayed death after cerebral fat embolism are described. The multiple and widespread embolic lesions consisted of variously-sized and irregularly-contoured foci of demyelination and necrosis as well as the anticipated petechial haemorrhages. Both grossly and microscopically, these lesions were so strikingly reminiscent of the residual plaques of multiple sclerosis that they not only suggested a mechanism of lesion formation (central infarction) but also pointed to a possible underlying cause (a disturbance in lipid metabolism). This second study consists of a three-fold investigation into the fields of geographical distribution of multiple sclerosis, the possibly significant clinical findings, and of the chemical evidence of alterations in the serum lipids which might explain the occurrence of the lesions of multiple sclerosis as well as the pathogenesis of endogenous (non-traumatic) fat embolism. Geographically speaking, multiple sclerosis seems to be more common in countries or areas (northern Europe, the low countries, Germany, Austria, and Switzerland) where the dietary intake of fat is high while, to the contrary, it is relatively rare in those areas (the Orient) in which the quantitative intake of fat is low. Whether the use of saturated versus unsaturated fat plays any important role in this regard is not yet known. From a clinical viewpoint, evidence of a disturbed lipid metabolism in patients with multiple sclerosis is less convincing. Other than for an occasional complaint of a relative intolerance of a heavy fat meal or digestion of fatty foods, about the most suggestive feature of multiple sclerosis in this respect is the progressive deterioration in weight, to terminate in a marked loss in the fatty tissues of the body. The unverified statement that patients on a low-fat diet have fewer and less severe exacerbations

of the disease may also prove to be significant. Experimental support for this possibility lies in the occurrence of a high chylomicron index in the blood serum in the cases of multiple sclerosis (Thienes). There is extant evidence which suggests a mechanism for the formation *in vivo* of endogenous lipid particles large enough to obstruct the small arteries and capillaries of the brain. This mechanism of endogenous fat embolism could, therefore, furnish a source for obstructing micro-embolisms of the white matter capable of producing the plaques of multiple sclerosis. Evidence which would further support this conclusion may be found in a plan of successful treatment during the acute exacerbations of the disease by dissolution of the occluding lipid particles through action of lipases. This aspect of the problem will be considered in the third paper of the series.

(Author's Abstr.)

Multiple Sclerosis as an Incidental Complication of a Disorder of Lipid Metabolism: III. Treatment by Heparin of Acute Exacerbations of the Disease.

This, the third and last paper in a series of studies on multiple sclerosis, attempts an evaluation of a new concept as to causation of this disease. This study has to do specifically with the treatment of the acute exacerbations of this disease with Heparin. This medication is recommended on the theory that the acute phases of multiple sclerosis are the result of lodgment of lipid particles in the arteriocapillary system of vessels of the white matter of the central nervous system. Because even small doses of Heparin are credited by biochemists with the ability to stimulate lipase activity, which should result in an increased breakdown of neutral fats, this substance has been tried in an effort to promote the dissolution of lipid thrombo-embolisms which, according to this hypothesis, are already obstructing these vessels. The apparently favourable results achieved by the present writer in a preliminary trial of repeated intravenous administration of small doses of this medication seems to warrant its further investigation at the hands of others. A regimen is suggested for this purpose.

(Author's Abstr.)

SEPTEMBER

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Spectrophotometric Studies on Urinary Constituents of Schizophrenic Subjects

1. A urine test is described which has permitted the correct prediction of diagnosis of schizophrenia with results which agree 85 per cent. of the time with the clinical diagnosis of this disorder.

2. Preliminary studies suggest that this test reflects a difference in metabolism of the amino acid, tryptophane.

(Authors' Abstr.)

Dartal in Treatment of Hospitalized Schizophrenic Patients

The results obtained in a controlled experiment to test the effect of Dartal on hospitalized schizophrenic subjects is here reported: One group of subjects received placebos, another group received a commonly-used tranquillizer while a third received Dartal. Although it is immediately apparent that neither Dartal or the commonly employed tranquillizer are cures for the schizophrenic process a favourable response occurred in the overall behaviour of the

patients receiving Dartal which was greater than in the placebo group and in the group which was given the other tranquilizer.

It is apparent that Dartal does not alter the course of the schizophrenic process although it does favourably influence a number of the individual signs and symptoms, i.e. associations, attention, awareness, feeling, mimetic expression, motor activity, speech and interest in work. It is of pertinence to note that three functions which are considered by most psychiatrists to be cardinal manifestations of the schizophrenic process, namely associations, attention and awareness were favourably altered by Dartal with a change approaching the individual norm or baseline. No change in these functions occurred in the group receiving placebos or the group receiving the other active compound.

No deleterious side-effects on blood pressure, liver function or blood forming organs were encountered in the patients receiving Dartal. Two patients receiving Dartal did show what was interpreted as a toxic manifestation consisting of a clinical picture closely resembling a Parkinsonian syndrome. However, this reaction completely disappeared after the drug was discontinued for 48 hours and did not again become manifest when the compound was resumed at a lower dose level.

The results here reported are based on a study of a numerically small group of subjects. There may be some variation in these results when large groups are similarly studied.

(Authors' Abstr.)

Convulsive Therapy Without Curarization in Severe Somatic Complications

The literature was reviewed to emphasize that for more than 15 years E.C.T., *per se*, without pre-medication, was found to be a safe and relatively simple procedure even when severe somatic or skeletal conditions complicated the psychiatric picture. Five cases of severe combined conditions were reported to illustrate this relative safety of unpremedicated E.C.T. where the skeletal, cardiorespiratory, and neurologic status were distinctly vulnerable. It was felt that in these cases curarization might have added to the treatment risk. Additional cases were presented to illustrate that curarization complicated the E.C.T. procedure and in three instances did not prevent the onset of post-treatment coronary thrombosis. These features were discussed in relation to further researches with electrocerebral therapy and in maintenance electroconvulsive therapy of chronic, relapsing psychoses.

The experience and responsibility of the individual psychiatrist should be the determining factor in the management of E.C.T. rather than general or "legal" subjection to complex curarizing anaesthesiologic procedures.

(Authors' Abstr.)

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Deprol in Depressive Conditions

Several new drugs have been introduced recently for the treatment of depressive conditions. Deprol, a combination of meprobamate and benactyzine, interested us because of the previously observed fact that meprobamate alone already possesses certain anti-depressive properties; particularly when administered in dosage higher than usually used in the treatment of anxiety conditions, and when given to patients who exhibit a certain amount of anxiety and tension, even if their psychomotor activity is slightly retarded. The addition of benactyzine is considered to be beneficial as it seems to relieve the ruminative obsessive aspects of the depressive mood.

In the series of patients suffering from varying degrees of depression, Deprol, in conjunction with milieu and various forms of psychotherapy, did benefit a considerable number of patients. The improvement under Deprol consisted mainly in lessening of general depressive mood without euphoria, producing more interest in the surroundings (libido extension), lessening of fear, apprehension, panic and anxiety and marked reduction of irritability, crying spells and insomnia. Patients who manifested marked delusions and hallucinations were least influenced. In a great number of the patients Deprol definitely facilitated psychotherapy while it was much less effective without it.

(Authors' Abstr.)

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Introductory Remarks

Today psychiatrists are about to take a good look at various phases of knowledge on nialamide. All research in medicine is designed to benefit the patient. The practitioner, who ultimately dispenses the agent, is an integral part of the process. Without him, medical research would be pure research and not applied research, as it is intended to be.

Those who have carefully and painstakingly assembled this knowledge, are the most prominent and erudite in their field and everyone is very grateful for their help and philanthropy.

The Eastern Psychiatric Research Association, officially incorporated four years ago, has a membership of nearly 200. This membership, among whom is the President of the American Psychiatric Association, Dr. William Malamud, is made up mainly of practising and research psychiatrists. The chief aim of the Eastern Psychiatric Research Association is the fostering of clinical studies on therapeutic methods, drugs and apparatus in psychiatry; and the presentation and publication thereof. Clinical study is there used in its broadest sense and includes not only the study of the effect of an agent on the patient's clinical condition but also chemical, pharmacologic and cognate investigations, all leading to a sound understanding of the agent, its indications and clinical effects, its chief site of action, its absorption, fate and excretion and its side actions.

At the meeting of the American Psychiatric Association in Philadelphia, a round table discussion entitled "Integration of Somatic Therapies in Psychiatry" the author had occasion to say a few words on electroshock therapy (E.C.T.) and drugs. He made special reference to depressed patients, electroconvulsive therapy and psychic energizers. There is no need to relate the extremely favourable clinical reports on these drugs by many of the original investigators; and of the expressed opinion of some that at last, after 20 years, they see the end of E.C.T. Some of these clinicians have practically abandoned E.C.T. in favour of the psychic energizers. Is this wholesale shift of therapeutic agents justified? Many will answer in the affirmative. But are they sure of their answer? No one will dispute, that today the most efficient and reliable therapeutic agent available for relief of depression is E.C.T. This modality is far more effective than any drug presently available. Its results are quick and long lasting. This cannot be said of the psychic energizers psychiatrists have been using. They yield results slowly, the number benefited is considerably less than with E.C.T. and to prevent relapse the drug has to be given for months upon months.

Since the advent of succinylcholine a few years ago E.C.T. has become the safest treatment in psychiatry. With psychic energizers there has always been the threat of liver damage and possibly death. To guard against this, the patient is subjected to repeated blood counts, urine and liver studies. The long duration of the treatment and the repetition of these tests make the treatment more costly than E.C.T. More important than the cost, is the fact that the patients are not relieved quickly and are subjected to a longer period of suffering.

The originator of E.C.T., Dr. Ugo Cerletti, who was recently in America, expressed the opinion that E.C.T. was a trying treatment and that since its inception he had been attempting to find a substitute. He has experimented with injections of emulsions of shocked pigs' brains. His results have been encouraging but not conclusive. Psychiatrists have, for a long time, wished that some day they might have an injection or a drug which would give comparable results to E.C.T. in both percentage of cures and rapidity and duration of improvement. Until such a drug becomes available they should not delude themselves by being over enthusiastic about any agent less effective than E.C.T. They should not become second-rate therapists: second rate because they are afraid to use an agent known definitely to be superior and substitute in its stead a second-best agent. Psychiatrists do hope that nialamide, now to be discussed, will prove to be the agent which they are looking for. Should this not be so, it is hoped that these studies will lead them to discover specific indications for its use at least in certain patients. They should be careful and conservative in passing judgment on any therapeutic agent; for undeserved over-enthusiasm may guillotine any beneficial effect it may have.

(Author's Abstr.)

A Pharmacologic Summary of Nialamide

Nialamide has been found to be a potent, specific, relatively non-toxic antidepressant with important features from a clinical point of view, that is, no adverse effect on liver function or postural hypotensive activity.

(Author's Abstr.)

Transaminase Controlled Nialamide

This report is concerned with the use of nialamide in 23 patients with various mental disturbances. These include reactive depression, manic-depressive insanity, involuntional melancholia, schizophrenia, psychopathic personality and barbiturate addiction.

On the basis of recent experience, it can be stated that nialamide is a good amine oxidase inhibitor which will induce remission of depression and apparently is free from serious side-effects.

Dosages with amine oxidase inhibitors were adjusted to levels that would not produce serious liver damage. This was done by means of sodium glutamic-oxaloacetic transaminase (SGO-T) determinations.

(Authors' Abstr.)

Nialamide for the Treatment of Anergy and Depression

The psychic stimulant, nialamide, in a study with 26 hospitalized patients was found to be therapeutically effective, comparable to previously investigated monoamine oxidase inhibitors. Nialamide was markedly effective in alleviating depression and/or anergy in 16 persons, restoring them to a higher level of psychic integration. Of the 16 cases, three were classed as recovered, five as much improved, and eight as improving. One patient showed sporadic improvement and nine were either unimproved or worse with nialamide. Side-effects were anxiety and akathisia in a total of four patients which were quickly relieved by concomitant administration of phenothiazines. Four patients experienced either a mild nausea and headache, transitory choreic movements, a syncopal attack or transitory diarrhoea. There was a slightly elevated BUN in one case. Later studies showed a transitory rise of alkaline phosphatase in one patient. There was no relief of pain in one case of angina pectoris. Evidence of postural hypotension was encountered in one patient. Nialamide appears to have little of any potentiating effect on other phrenotropic drugs. There were no serious untoward effects observed in this study. In addition to alleviation of the anergy and/or depression in 16 patients, there was a complete loss or marked lessening of delusional and hallucinatory content in nine of these.

From the data obtained in this exploratory study with nialamide, it is apparent that this monoamine oxidase inhibitor is a safe, fairly rapid antidepressive and alerting agent; plus beneficent effects on ideation and perception. It alleviated the symptoms in approximately 60 per cent. of hospitalized depressed and anergic patients without apparent relationship to the diagnostic category, the number of previous admissions, the duration of the present illness, the age of the patient, or the severity of the anergy or depression.

(Authors' Abstr.)

Effect of Amine Oxidase Inhibitors on the Conditional Psychogalvanic Reflex in Man

1. Successful response to treatment with amine oxidase inhibitors is associated with diminution in magnitude of the conditional psychogalvanic reflex responses without alteration in differentiation. In most cases the unconditional psychogalvanic reflex is diminished as well.

2. The neurophysiologic and psychophysiologic implications of this finding are discussed.

3. The diminution of the conditional psychogalvanic reflexes is related to dosage, duration of administration and treatment results.

4. Testing of the conditional psychogalvanic reflex is recommended as a means of evaluating adequacy of dosage with amine oxidase inhibitors.

(Authors' Abstr.)

Treatment of Depressive States in Ambulatory Patients

Nialamide, an amine oxidase inhibitor, is a new antidepressant which was prescribed for 100 ambulatory patients (ages 22 to 72) whose essential complaints were depressive symptoms. There were 32 manic-depressives, 17 involuntional melancholics, 15 schizophrenics with depressive features and 36 neurotic depressives in this study.

Severely depressed individuals were started on nialamide 25 mg. three times a day and moderately ill patients were given 10 mg. three or four times daily. If after one week there was no improvement the dosage was increased by increments of 10 to 25 mg. a day until improvement occurred or until the dosage was 200 mg. daily.

Phenothiazine tranquilizers and barbiturates were combined with nialamide whenever the depression was accompanied by anxiety, agitation, panic, anorexia and insomnia, marked psychosomatic symptoms, paranoid colouring, or when the depression immediately followed physiological or psychological shock. This combined treatment also was prescribed routinely for all depressed schizophrenics.

Nialamide was given in conjunction with E.C.T. to 16 suicidal patients. This combined treatment was safe but did not reduce the number of shock treatments required.

Side-effects such as headaches (10 per cent.), dry mouth (4 per cent.), sweating (4 per cent.), dizziness (3 per cent.), constipation (3 per cent.), blurred vision (2 per cent.), hypotension (2 per cent.), epigastric distress (1 per cent.) and oedema (1 per cent.) occurred with doses in excess of 100 mg. daily. These were mild and did not necessitate the discontinuation of nialamide. This drug did not cause postural hypotension nor many of the other side-effects produced by other antidepressants.

At the end of eight weeks nialamide therapy 21 patients were improved and 30 were partially improved. Of the 49 treatment failures, 29 patients had a good prognosis and 20 had a poor prognosis. To achieve therapeutic benefit 50 to 75 mg. of nialamide daily was necessary. An occasional patient required as much as 150 mg. daily. Larger doses did not increase therapeutic benefit but were likely to produce side-effects.

Although therapeutically active, nialamide is somewhat less effective than other anti-depressants used for the same target symptoms and assessed by similar criteria for benefit. On the other hand because nialamide is well tolerated by patients in every age group and particularly because it apparently does not cause postural hypotension it is safe for the treatment of ambulatory depressed patients by general practitioners and specialists other than psychiatrists.

(Authors' Abstr.)

Effectiveness and Tolerance of Nialamide for Geriatric Patients

Nialamide was studied in three groups of patients to establish dosage, effectiveness and safety. In depressed geriatric hospitalized patients, 25 mg. three times daily is sufficient for therapeutic effectiveness with minimal occurrence of untoward reactions. For agitated hospitalized patients and ambulant patients with the anxiety state, nialamide was not found effective with the 75 mg. dose used.

(Authors' Abstr.)

Clinical Experiences with Nialamide in Depression

What conclusions can be drawn from this series of 50 cases? First, nialamide seems to offer considerable promise in the treatment of certain depressive reactions. It seems most useful in the treatment of neurotic-depressive reactions in patients under 50, and it is of benefit in some patients with depressions of the manic-depressive type. In the older patients suffering from depression, it seems more useful in males than in females. I am unable to explain these differences clinically. Nialamide is remarkably non-toxic as side-effects are very few and minimal. Certainly nialamide seems to be a useful addition to the psychopharmacologic armamentarium.

(Author's Abstr.)

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Treatment of Depressions in Private Practice with Imipramine

There were 305 patients in 369 diagnostic entities, given imipramine in dosages varying from 25 mg. to 200 mg. daily. Patients were selected on the basis of the presence of depression or symptoms indicative of a basic depression. Other therapies were used as indicated.

Improvement varied from 36.75 per cent. in those patients who received an initial daily dosage of 25 mg. to 71.4 per cent. in those patients receiving an initial daily dosage of 100 mg. Only those patients who were able to return to their former state of relative well-being were considered improved. The majority of patients were able to discontinue medication in six months, others needed continuation of medication over a period of two years. These latter patients were usually able to continue their state of improvement on a reduced dosage.

Side-effects were generally mild and did not contradict the continuation of the medication. The more severe reactions usually responded to reduction of dosage or by the administration of a tranquilizer.

On the basis of the results obtained, imipramine has excellent properties as an anti-depressant without serious side-effects.

(Authors' Abstr.)

A Clinical Study of the Anticonvulsant Properties of Meratran

A group of 40 epileptic patients who had previously received only phenobarbital as an anticonvulsant were divided into two comparable groups in regard to age, I.Q. and sex. One

group was given Meratran therapy; both groups continued phenobarbital therapy at the same dosage level they had been receiving prior to this study.

Statistical analyses indicate that clinically Meratran exhibits a significant anticonvulsant effect and simultaneously overcomes some of the soporific effects of phenobarbital.

Further indications of the anticonvulsant activity of Meratran were found clinically in a small group of patients who had received combinations of phenobarbital and one or more of the other anticonvulsants prior to and during Meratran therapy. The greatest reduction in seizures during treatment with Meratran occurred in this group.

Central stimulating effects of Meratran therapy, when present, were for the most part favourable: increased alertness, less drowsiness, increased motor activity. Undesirable side-effects occurred in two patients whose pre-Meratran psychiatric condition indicated a tendency to anxiety or hallucinations.

(Authors' Abstr.)

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The Contributions of Enzymology to Neurochemistry

It is evident as they survey the field of neurochemistry today that the enzymological approach is exercising considerable influence on the minds of those who seek a relation between mental activity and brain chemistry. It has always been the author's belief that such a relation must exist, and this belief has dominated his own investigations in the neurochemical field since he first became acquainted with mental disorder problems nearly thirty years ago. The subject of neurochemistry in relation to mental behaviour has grown rapidly since then in spite, perhaps, of a variety of psychiatric dogmas. It is now developing vigorously and fruitfully, so much so that he feels justified in claiming that in the enzymological approach to neurochemistry they have one of their finest tools for the exploration of the processes of the mind.

(Author's Abstr.)

The Effect of LSD on the Associative Processes

1. The responses of 25-LSD subject to the word association test employed by Rapaport, Gill and Schafer have been compared to those of a control group and to the responses given by groups of schizophrenic, depressive, and neurotic patients tested by Rapaport *et al.*
2. Our analysis shows that in the associative processes, at least, the LSD reaction does not closely approximate any of the principal "functional" psychiatric disorders.
3. Probably the most striking way in which the LSD reaction differs from all other conditions is the abolition of the differential response to traumatic and non-traumatic stimuli. We have attempted to place this phenomenon within the framework of modern ego-psychology theory.

(Authors' Abstr.)

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The Value of Photic Stimulation in the Diagnosis of Epilepsy

1. A total of 1,366 patients with unquestionable or suspected epilepsy and non-paroxysmal routine EEGs were exposed to photic stimulation.

2. In 11·2 per cent. of the cases paroxysmal activity was excited. Positive responses were most frequent in the group of cryptogenic epilepsy (24·7 per cent.) and less common in that of symptomatic epilepsy (6·7 per cent.).

3. Photoc stimulation was most effective in the younger age groups and in patients with abnormal routine EEGs.

4. In the group with cryptogenic epilepsy there was a higher proportion of paroxysmal reactions in females than in males.

5. Flicker frequencies of 12 and 14 f/s were most effective. ETM resulted in an increase in positive results, particularly in adult patients.

6. In 44 cases, responses occurred which must be regarded as non-specific.

(Author's Abstr.)

Studies on Human Saliva: a Tyramine-like Component and Its Response to Autonomic Stimulation

A tyramine-like compound has been detected as a component of human mixed saliva.

The secretion of this compound is apparently regulated by the autonomic nervous system, as seen by the changes in concentration following a single injection of autonomic drugs in human subjects.

Injection of urecholine gives rise to a definite response curve. Epinephrine also elicits changes in concentration, but not as uniformly as does urecholine.

There is no consistent correlation between changes in salivary flow volume and concentration of this salivary component.

The application of these preliminary findings to the study of autonomic function in man is discussed.

(Authors' Abstr.)

Psychological Studies of Korsakoff's Psychosis: I. General Intellectual Functions

1. The Wechsler-Bellevue Intelligence Scale and the Wechsler Memory Scale were administered to two groups of patients with the Wernicke-Korsakoff syndrome secondary to alcoholism. The first study included observations of 15 patients, who were tested shortly after the onset of their illness and then at periodic intervals ranging from three weeks to 12 months. The second study was restricted to a group of 22 patients who had all reached the relatively stable and chronic phase of the disease and who were tested at periods ranging from 12 months to over 12 years after the acute phase of the illness.

2. The test results disclose a characteristic pattern of cognitive deterioration in the Wernicke-Korsakoff syndrome. There is, however, no evidence that this pattern is specific to this syndrome. The relative degree of deterioration in different cognitive functions changes with the progress of the disease, more particularly as the initial symptoms of general confusion clear up. Presumably because of this differential progress no stable profile of intellectual functioning could be determined for the disease.

3. Memory functions clearly suffer more severely than other cognitive processes, and the most marked and persistent defect is the low capacity for learning new associations or the retention of newly-presented information such as short stories. This failure is particularly marked in tests or situations which require the reproduction of chronological sequences. The clinical disability of Wernicke-Korsakoff patients is largely accounted for by these defects.

4. The results of this study agree in general with previous reports of mental deterioration in Korsakoff's psychosis. However, attention is drawn to the defects in cognitive functions other than those directly dependent on retentive memory. The data also stress the gradually changing character of the mental abnormality, from the onset of the disease to the late stable stage.

5. Results obtained by the standard psychological tests used in these studies can only serve for a preliminary or tentative determination of the psychological profile of this disease. We have therefore regarded the conclusions presented here as a point of departure for a more intensive research geared specifically to an investigation of this cognitive damage in Korsakoff's psychosis. The results of this investigation as well as our observations on confabulation will be presented in future publications.

(Authors' Abstr.)

An Exploratory Investigation of the Effect of Meprobamate on Stuttering Behaviour

Ten stutterers given 600 mg. of meprobamate per day for the first week, 1,200 mg. per day for the second week, 1,600 mg. per day the third week, and 2,000 mg. per day the fourth week showed a reduction in the mean number of stuttered moments. This reduction, while not achieving statistical significance, did show a definite trend and was significant at the ·10 level of confidence for the group that received meprobamate. Non-parametric statistics revealed a statistically significant amount of progressive success with each trial for this group. Their own subjective evaluations confirmed the findings. On the basis of these results, further study is indicated.

(Authors' Abstr.)

Some Factors Associated with Concordance and Discordance with Respect to Schizophrenia in Monozygotic Twins. *Rosenthal, D.* 1

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A New Drug Causing Symptoms of Sensory Deprivation

Neurological, electroencephalographic and pharmacological data have been presented on over 100 individuals who have been treated with Sernyl, a drug that appears to exert a blocking action on the thalamus and midbrain. This drug eventually produces a blocking of all forms of sensation with pain sensation disappearing first. Motor movement is not impaired, except for ataxia, until the patient becomes unconscious. Blood pressure and reflexes are increased and vertical nystagmus appear in high dosage of the drug. Early and sometimes prolonged symptoms appear that are similar to those reported in sensory deprivation studies; namely, anxiety, illusional, delusional and hallucinatory phenomena with a feeling of displacement. Interference with thinking processes is an early complaint. It is concluded that Sernyl produces a "centrally medicated" sensory-deprivation syndrome.

(Authors' Abstr.)

Blood and Urinary Serotonin and 5-Hydroxyindole Acetic Acid Levels in Schizophrenic Patients and Normal Subjects

The mean concentration of blood serotonin in normal non-psychotic male subjects was found to be 0.19 µg./ml., in chronic schizophrenic male patients 0.17 µg./ml., and in acute psychotic male patients 0.12 µg./ml. The mean urinary excretion rate of 5-HIAA in normal male subjects was found to be 203 µg./hour, in chronic schizophrenic male patients 225 µg./hour, and in acute psychotic male patients 332 µg./hour. The results do not indicate a metabolic defect in serotonin metabolism and therefore do not support the hypothesis of a causal relationship between serotonin metabolism and acute or chronic schizophrenia.

(Authors' Abstr.)

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The Influence of Chlorpromazine on Pathologic Emotions and Sexual Unrest

The effective use of drugs in psychiatric treatment requires specific knowledge of the influence of pharmacologic agents on emotions and related psychodynamic factors which may markedly influence the clinical state of any patient. When attention is paid to these features, it is possible to develop a useful scheme, which not only deepens the understanding of the nature of clinical changes induced with drugs, but also allows for the selection of the correct method of treatment for an individual patient in a particular phase of an illness.

This study reports the effects of chlorpromazine in a series of 142 patients who received the drug as an adjunct to intensive psychotherapy in a hospital setting. Good therapeutic results were obtained in patients demonstrating fear, hostility, or related paranoid features. Contrary to general opinion, chlorpromazine appeared to be singularly ineffective in many conditions where anxiety was a leading feature. The marked ability of chlorpromazine to reduce sexual unrest has received very little recognition, yet this influence may contribute substantially to its broad clinical usefulness in the treatment of psychiatric disorders.

(Authors' Abstr.)

The Metabolism of Mescaline with a Note on Correlations Between Metabolism and Psychological Effects

Eleven volunteer subjects were given mescaline intravenously in twenty experiments. For the period of intoxication blood levels and rates of urinary excretion of mescaline and trimethoxyphenylacetic acid were measured and observations made of the subjects' behavioural responses.

The behavioural responses of the subjects varied widely in severity of symptoms and in the pattern of disturbance of mental function.

An average of 31 per cent. of the drug administered was recovered in the urine within the first six hours after the administration of the drug. An additional 7.4 per cent. (average) of the administered drug was recovered as trimethoxyphenylacetic acid.

The blood levels and rates of excretion of mescaline did not fall off asymptotically, but formed a flattening curve and often one with some elevation between the third and sixth hour after administration of the drug. The blood levels and rates of excretion of trimethoxyphenylacetic acid showed such secondary peaks to an even greater extent.

The period of maximal behavioural changes followed the period of maximal blood level and excretion by one to two hours.

No correlations were observed between degree or type of behavioural responses and blood levels or rates of excretion of mescaline.

The curves of blood levels and rates of excretion of mescaline and trimethoxyphenylacetic acid and the delay in occurrence of maximal behavioural change suggest that mescaline may be converted into some other substance which is directly responsible for the effects on the central nervous system.

(Authors' Abstr.)

An Evaluation of the Therapeutic Use of Triflupromazine in Mental Disease

Examination of the results of this investigation leaves no doubt that triflupromazine is an effective and useful phenotropic agent. This seems a particularly valid conclusion when the nature of the patient group is considered. All patients treated were classified as chronically ill and were considered to have relatively poor prognosis. Side by side comparison with chlorpromazine in this series of 124 patients showed triflupromazine at least to equal the effectiveness of the older drug. It is likely that if chlorpromazine had been administered by other than a blind technique larger doses would have been prescribed. With regard to potency, our impression is that for equal therapeutic effect, the dosage of triflupromazine should be approximately one-quarter or one-fifth that of chlorpromazine. Few patients required a dosage in excess of 100 mg. of triflupromazine daily and some were adequately maintained on 50 mg. daily. Toxic central nervous system reactions, in our experience, seldom occurred unless the daily dosage exceeded 200 mg.

The battery of psychological tests employed in this investigation confirmed the clinical finding that triflupromazine produced significant improvement in this series of hospitalized patients. The techniques adopted were such as to preclude the possibility that the changes observed were the result of chance. The inclusion of a placebo group provided an objective estimate of changes due both to the increased attention received by patients involved in this study and to the psychological effects of the ritual of taking medicine.

(Authors' Abstr.)

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A Cerebrospinal Fluid Bank. <i>Voris, H. C., and Talso, P. J.</i>		252

Slowness in Schizophrenia

The influence of various factors on the mental speed of a group of schizophrenic patients was investigated by means of the Nuffern speed test. Longer duration of illness was associated with slower performance on the unstressed portion of the test, this being more definite in the case of those patients who also showed inappropriate affect. Patients who had had physical treatment tended to be slower on the unstressed portion of the test and those whose illness had a favourable outcome tended to be faster than the others. A significant relationship appeared between low stress-gain score and favourable social outcome. No satisfactory formula for predicting outcome on the basis of this test could be devised. An effort to correlate speed with disease and recovery failed because of the difficulty of finding patients who had gone through their illness without receiving physical treatment, since this latter formed a complicating factor which could not be allowed for.

(Authors' Abstr.)

The Use of an Object Sorting Test in Elucidating the Hereditary Factor in Schizophrenia

A significant number of parents of schizophrenics with "thought disorder" were found to obtain scores on the sorting test of Rapaport (1945) different from those of control normals but similar to those found in schizophrenic patients.

It is suggested that this test may provide an objective means of estimating the presence of "schizoid" features in the relatives of schizophrenics, and thus aid in the elucidation of the hereditary factors in schizophrenia.

(Author's Abstr.)

A Clinical and Biochemical Study of a Trial of Iproniazid in the Treatment of Depression

A controlled trial of iproniazid on 50 patients with depression showed that 26 of them improved and that the improvement in at least 12 of these was due to the drug. The danger of liver damage was stressed.

An attempt was made to differentiate these groups and to determine the mode of action of iproniazid in those patients who responded. Methods used included parenteral administration of 5-hydroxytryptophan and 3,4-dihydroxyphenylalanine and assessment of urinary 5-hydroxyindole excretion.

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Tryptophan Metabolism in Porphyria, Schizophrenia, and a Variety of Neurologic and Psychiatric Diseases

The urinary excretion of 9 metabolites of the essential amino acid L-tryptophan has been determined in 18 patients with acute, chronic, or mixed hepatic porphyria, 19 patients with schizophrenia, 8 patients with a variety of psychoses, and 10 patients with a variety of neurologic diseases. Of 18 patients with porphyria, 13 showed evidence of abnormal tryptophan metabolism characterized by increased urinary excretion of kynurenine, acetylkynurenine, kynurenic acid, hydroxykynurenine, and occasionally, xanthurenic acid or other metabolites. A similar metabolic response was found in 6 of the patients with a variety of types of psychoses. Each of the patients with neurologic conditions metabolized tryptophan in an essentially normal manner.

Although the type of abnormality of the tryptophan metabolism of these patients suggests a functional pyridoxine deficiency, neither biochemical nor clinical improvement resulted following pyridoxine supplementation. Both clinical and biochemical improvement were often observed following treatment with chelating agents.

The possibility that the clinical and biochemical manifestations of porphyria might be related to a disturbance in polyvalent cation balance was discussed.

(Authors' Abstr.)

The Effects of Lysergic Acid After Cerebral Ablation

The observations reported above are typical of 70 experiments conducted over a two-year period. In these tests, all animals were used in various combinations. According to these observations, the young chimpanzee reacts to lysergic acid with a panorama of abnormal behaviour which is consistent and characteristic. If such an animal is subjected to bifrontal lobectomy, his reactions in ordinary situations are radically changed; yet his reactions to the drug are not. Paradoxically, he reacts to lysergic acid in the same way as before operation,

although this massive ablation has obviously affected all other reactions in social, test, and training situations. Indeed, among his various post-operative responses, only the drug reaction remains comparable to those observed before bifrontal lobectomy. Apparently, intact frontal lobes are not essential for the characteristic drug reaction.

On the other hand, if such an animal is subjected to bilateral temporal lobectomy, his responses to ordinary situations are remarkably unchanged, except for a four-week period after surgery. Yet, his response to the drug is obviously changed. Some autonomic reactions remain thereafter, but panic or perceptual aberration does not increase in the post-operative drug reaction. However, unilateral temporal lobectomy does not change the animal's reaction to lysergic acid. Nor does lobectomy alter social or training responses. Apparently, one or the other temporal lobe is essential for this drug reaction in young chimpanzees.

When the temporal ablation includes only the mesial structures, the reaction to lysergic acid is unchanged. Yet, after selective ablation of both lateral temporal cortices, the reaction changes or disappears. Perhaps the lateral temporal cortex and its tapetal connections form essential links in the neurologic chain which constitutes the background of this panoramic reaction.

The reaction itself is a compound of perceptual aberration and panic. As the animal reacts, he may look at his hand and scream. Then his pupils dilate, and his hair stands on end. Or he will react abnormally to the usual forms, colours, and sounds of his habitual surroundings.

According to recent reports, the lateral temporal cortex is concerned with perception. The human reaction and the reaction of the chimpanzee to administration of lysergic acid are certainly characterized by gross perceptual aberration in the chimpanzee. Perhaps the drug disturbs perceptual mechanisms represented in the grey mantle of the temporal lobe.

(Authors' Abstr.)

Effect of Drugs on Discharge Characteristics of Chronic Epileptogenic Lesions

Chronic epileptogenic lesions were produced in the visual cortex of rabbits. The effect of anticonvulsant agents was measured against the discharge frequency of the spike focus, the threshold to photic activation, and the characteristic patterns of spread. A standard Metrazol challenge was used as a means of comparing our results with those obtained in the more usual pharmacologic assays. Dilantin did not produce suppression of the primary focus nor did it appear to limit spread to the basal diencephalon or to protect against Metrazol challenge. However, transcortical propagation was effectively limited.

Spirodione demonstrated effective suppression of the primary focus as well as limitation of spread both to basal nuclei and transcortically. Some protection also existed against Metrazol challenge. Tridione also appeared to suppress the primary focus as well as to limit spread to the basal diencephalon. However, transcortical spread was not effectively limited until the primary focus itself was suppressed. Metrazol protection was the highest of any of the drugs tested. Phenobarbital produced only slight suppression of the primary focus and transcortical spread, good limitation of spread to the basal diencephalon, and good Metrazol protection.

(Authors' Abstr.)

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The Psychiatric Application of Vesprin

Vesprin is an effective phenoprazic drug of the broad spectrum type comparable to chlorpromazine in its general applications. It is more effective and less toxic than chlorpromazine and should be considered the first choice for the treatment of schizophrenic conditions and the obsessive-compulsive neurosis. It is of value in the treatment of senile psychosis and valueless in the treatment of depressions and of manic psychosis—except, in the latter case, as an antikinetic. The drug is almost free from severe side-effects and complications. It interferes less than chlorpromazine with the blood-pressure-regulating mechanisms of the body, but produces a substantial amount of extrapyramidal reactions. Of these last, akathisia is the most bothersome, and this limits the usefulness of the medication in ambulatory neurotics.

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Relationships of Psychotomimetic to Anti-Serotonin Potencies of Congeners of Lysergic Acid Diethylamide

1. The psychotomimetic potency of 13 congeners of LSD-25 has been approximately determined in man.
2. With the exception of acetylation of the indole nitrogen, all the changes made in the LSD molecule reduced psychotomimetic potency. Bromination at carbon 2 caused the greatest inactivation.
3. High potency as a serotonin antagonist in isolated smooth muscle preparations was not correlated with high potency as a psychotomimetic.
4. The data do not support but do not disprove the "serotonin deficiency" hypothesis of the LSD psychosis.

(Authors' Abstr.)

Comparison of the Reactions Induced by Psilocybin and LSD-25 in Man

1. The reaction induced by oral administration of 57 to 114 mcgm./kg. of O-Phosphoryl-4-hydroxy-N-dimethyltryptamine (psilocybin) has been compared with that induced by a placebo and LSD-25 (1.0 to 1.5 mcgm./kg.) in 9 subjects.
2. Both LSD and psilocybin caused elevations in body temperature, pulse and respiratory rates, and systolic blood pressure. Threshold for elicitation of the knee-jerk was decreased by both drugs.
3. After both drugs, abnormal mental states characterized by feelings of strangeness, difficulty in thinking, anxiety, altered sensory perception (particularly visual), elementary and true visual hallucinations, and alterations of body image were reported by the subjects.
4. The effects of psilocybin did not persist as long as those of LSD.
5. LSD is 100 to 150 times as potent as psilocybin.

(Author's Abstr.)

Lithium in Psychiatric Therapy. Stock-taking After Ten Years

Lithium therapy is effective against manic phases of the manic-depressive psychosis; in protracted or frequently recurring mania it seems to offer advantages over other available therapies. Lithium salts are administered orally; they may be given alone or as a maintenance treatment after electric convulsive therapy.

Lithium is potentially toxic, and overdosage may lead to injury of the kidney tubules. A high sodium intake accelerates renal elimination of lithium and serves to protect the organism against intoxication.

Patients suffering from renal or cardiac disease should not be given lithium. In patients receiving lithium the dosage must be regulated according to individual tolerance, and one must make sure that the sodium intake is sufficient and remains sufficient. The patients should be supervised clinically and biochemically.

(Author's Abstr.)

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Obesity and the Denial of Hunger

The relationship of gastric motility to the experience of hunger has been investigated. In accord with traditional views a group of non-obese women usually reported hunger during contractions of the empty stomach, and no hunger in the absence of such contractions. A group of obese women, on the other hand, usually failed to report hunger during the presence of stomach contractions. This denial of hunger extended to a denial of sensations of epigastric emptiness and of the desire to eat—fundamental characteristics of the hunger experience among non-obese women. That the denial of hunger was due to a specific difficulty in discrimination in the presence of gastric motility is suggested by the observation that there was no difference between obese and non-obese women in the distribution of hunger reports in the absence of gastric motility.

Obese subjects manifesting the "night-eating syndrome" showed a significantly higher incidence of denials of hunger than did obese persons not manifesting this syndrome.

The suggestion is made that denial of hunger occurs in persons with a conflict over eating who are simultaneously subjected to strong social pressures in this regard. Its function, according to this hypothesis, would be to exclude from awareness any stimuli that signal an approaching caloric deficit with its concomitant conflict over eating.

(Author's Abstr.)

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